Intramolecular epoxidation using oxone

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1996

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University of Bath

Intramolecular Epoxidation using Oxone®

Submitted by Paul Andrew Clarke
for the degree of Ph.D. of the University of Bath
1996

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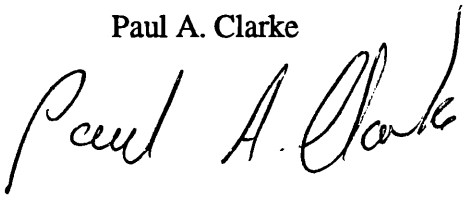

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To Mum and Dad,

for the constant love and support they have given over the last 26 years.

Contents

Acknowledgments

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Abstract

An attempt to use the ketone carbonyl group to direct the intramolecular epoxidation of alkenes by formation of a dioxirane intermediate is detailed in this thesis. Chapter One provides a short review of the epoxidation chemistry of dioxiranes and it surveys the literature in the area of directed epoxidation reactions.

Chapters Two and Three of this thesis describe the effect that a ketone carbonyl group has on directing the epoxidation of cyclic keto-alkenes by reagents that include *m*CPBA and DMDO. In both of these cases a remarkable *syn*-selectivity in the epoxidation process is observed. ^{18}O labelling studies show that a dioxirane intermediate is not responsible for the selectivity.

Attempts to use the reagent Oxone® in a biphasic system to form a dioxirane for the intramolecular epoxidation reaction are detailed in Chapter Four. This Chapter also describes investigations into the mechanism of this reaction. These investigations show that the oxidation of the ketone occurs in the aqueous phase and hence the lipophilicity of the ketone used is of critical importance in the epoxidation reaction. This work also suggests that the quaternary ammonium salt used in the reaction acts not as a phase transfer catalyst but as a surfactant. Both of these ideas are contrary to the generally accepted mechanism of the ketone - Oxone® biphasic epoxidation reaction. The consequences for intramolecular and intermolecular dioxirane epoxidation are discussed. Chapter 5 summarises the overall conclusions from the work in this thesis. Chapter Six contains a formal account of experiments and procedures.

Abbreviations

acac	acetylacetonate
b	broad
Boc	benzyloxycarbonyl
Bn	benzyl
n-Bu	normal butyl
^{t}Bu	*tert*-butyl
d	doublet
DCC	1,3-dicyclohexylcarbodiimide
DIBAL	di*iso*-butylaluminiumhydride
DMDO	dimethyldioxirane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EDTA	ethylenediaminetetraacetic acid
Et	ethyl
GC	gas chromatography
HOBT	hydroxybenzatriazole
IR	infra red (spectroscopy)
*m*CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MMPP	magnesium monoperphthalate
MS	mass spectrometry
NaHMDS	sodium hexamethyldisilazide
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance (spectroscopy)
nOe	nuclear Overhauser effect
OAc	acetate
Ph	phenyl
Pr	propyl

PTC	phase transfer catalyst
q	quartet
QAS	quaternary ammonium salt
s	singlet
t	triplet
TBAHS	tetrabutylammonium hydrogensulfate
TBA-Ox	tetrabutylammonium Oxone®
TBHP	*tert*-butyl hydroperoxide
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMDO	trifluoromethyl(methyl)dioxirane
TMEDA	*N, N, N', N'*,-tetramethylethylenediamine
TMSCl	chlorotrimethylsilane
TMSI	iodotrimethylsilane
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TsOH	*para*-toluenesulfonic acid

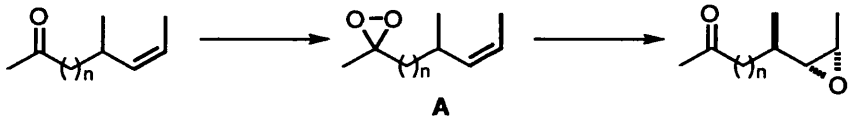
Chapter 1:

Background

1.1: Introduction

The control of relative stereochemistry has become of great importance in organic synthesis. Over the years many powerful methods have been developed that afford high stereoselectivity *via* intramolecular delivery of the reagent.[1] One reaction that has been examined extensively due to its synthetic utility, is the epoxidation of alkenes. It has been found that certain functionality can be used to direct epoxidation, and an overview of this will be presented later.

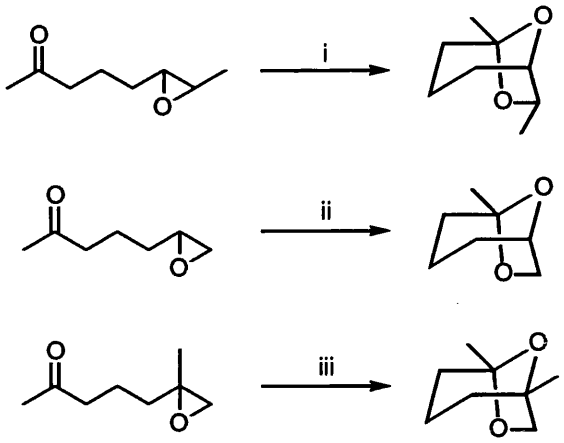
The aim of the work presented in this thesis is an attempt to use a ketone carbonyl group to effect intramolecular epoxidation *via* a dioxirane intermediate (**A**, Scheme 1). If an asymmetric centre within the molecule between the carbonyl and the alkene could control the face of the double bond epoxidised then the reaction would be made diastereoselective.



A

(Scheme 1)

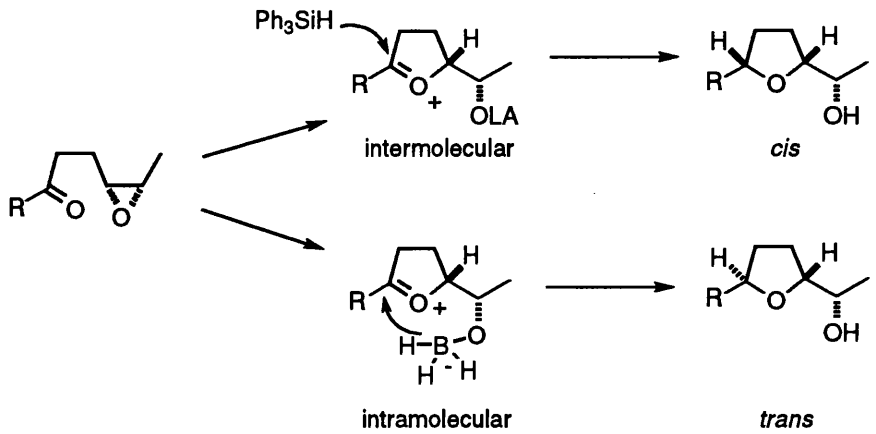
The resulting keto-epoxides are very useful synthetic intermediates. Wasserman has shown that these molecules cyclise to form bicyclic ketals[2,3] (Scheme 2). The cyclisation was achieved simply by Lewis acid or TFA catalysis and intramolecular trapping of the resulting oxocarbenium ion, by a hydroxyl group.



Reagents and Conditions: (i), CF_3COOH; (ii), $SnCl_4$; (iii), Heat on basic support.

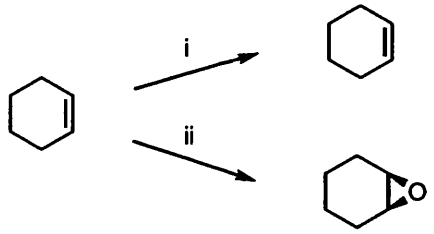
(Scheme 2)

Functionalised THF and THP rings can also be accessed from keto-epoxides.[4] If the keto-epoxide is treated with a nucleophile such as triphenylsilane and a Lewis acid, *cis*-THFs can be isolated (Scheme 3). If, however, borane-dimethylsulfide complex, which can act as both a Lewis acid and a nucleophile, is used then *trans*-THFs are predominantly formed (Scheme 3). These THF and THP units are present in many highly functionalised, biologically active polyether antibiotics such as monensin A and lasalocid. Carbonyl directed epoxidation would provide a highly attractive and efficient way of synthesising the key structural units present in these interesting molecules in a stereocontrolled manner.



(Scheme 3)

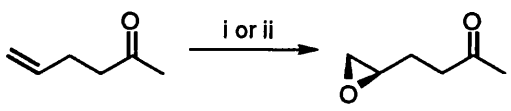
At the outset of this work there was a paper by Curci that seemed to support the idea of intramolecular dioxirane epoxidation.[5] This paper showed that organic soluble alkenes could be epoxidised in a biphasic mixture of CH_2Cl_2 (or benzene) and water with acetone, Oxone® and a phase transfer catalyst (either Bu_4NHSO_4 or 18-crown-6). In the absence of acetone no epoxidation took place (Scheme 4). Curci proposed that the acetone was being oxidised to a dioxirane. It was this dioxirane which was responsible for alkene epoxidation in this system.



Reagents and Conditions: (i), Oxone®, $EDTANa_2$, CH_2Cl_2, Bu_4NHSO_4, 1M NaOH, Phosphate buffer pH 7.2; (ii), as (i) but with acetone.

(Scheme 4)

In the same paper it was shown that hex-5-en-2-one could be epoxidised using Oxone® under pH control (pH=7.5) with or without acetone (Scheme 5). Curci suggested that the molecule's own carbonyl group was forming a dioxirane which was then carrying out the epoxidation. It is not possible to say whether this epoxidation was intra- or intermolecular due to the lack of any stereochemical marker within the molecule. We reasoned that we could use this biphasic method to investigate the stereochemical outcome of intramolecular epoxidation of organic soluble keto-alkenes (Scheme 1). Before describing the results of our study, the literature of two important areas will be briefly surveyed: first, the epoxidation chemistry of dioxiranes, and second, directed epoxidation reactions. The coverage of dioxirane epoxidation chemistry will be brief since several more comprehensive reviews have been published in the literature by Adam,[6] Murray[7] and more recently Curci.[8]

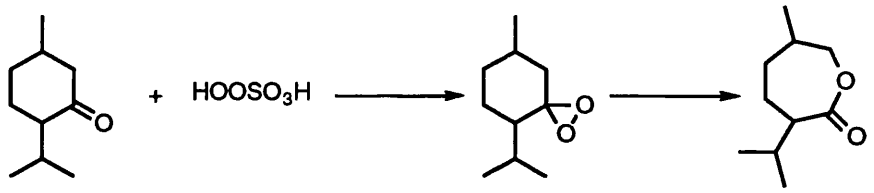


Reagents and Conditions: (i), Oxone®, $EDTANa_2$, 1M NaOH, Phosphate buffer pH 7.2; (ii), as (i) but with acetone.

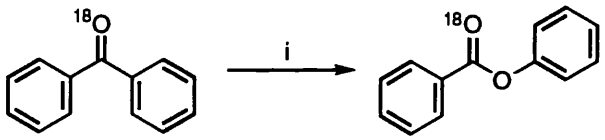
(Scheme 5)

1.2: Epoxidation Chemistry of Dioxiranes

Dioxiranes, the smallest of the cyclic peroxides, were first proposed as an intermediate by Baeyer and Villiger in the conversion by caroate† of menthone into its lactone,[9] an oxidation which now bears their names (Scheme 6). The intermediacy of dioxiranes in the Baeyer-Villiger oxidation, albeit using a different oxidant, was later disproved by von Doering and Dorfman in labelling experiments on benzophenone.[10] They found that when a ketone having an ^{18}O label in the carbonyl group was subjected to Baeyer-Villiger oxidation using *m*CPBA, the ^{18}O label was found entirely in the carbonyl group of the ester product (Scheme 7). If a dioxirane were to have been involved then the label would be expected to be in the ester oxygen as well.



(Scheme 6)



Reagents and Conditions: (i), *m*CPBA.

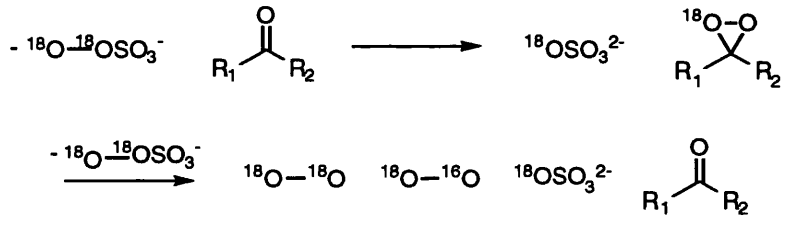
(Scheme 7)

One of the first indications that dioxiranes may exist came from experiments by Montgomery in the early 1970's. It was shown that certain ketones accelerated the decomposition of caroate, as well as the oxidation of chloride to hypochlorite by caroate in basic solution.[11] Acetone was shown to accelerate the decomposition of caroate by a factor of ten, cyclohexanone by 94 times and *N,N* dimethyl-1,4-oxopiperidinium nitrate by 14000 times. This study also showed that only small quantities of ketone were needed

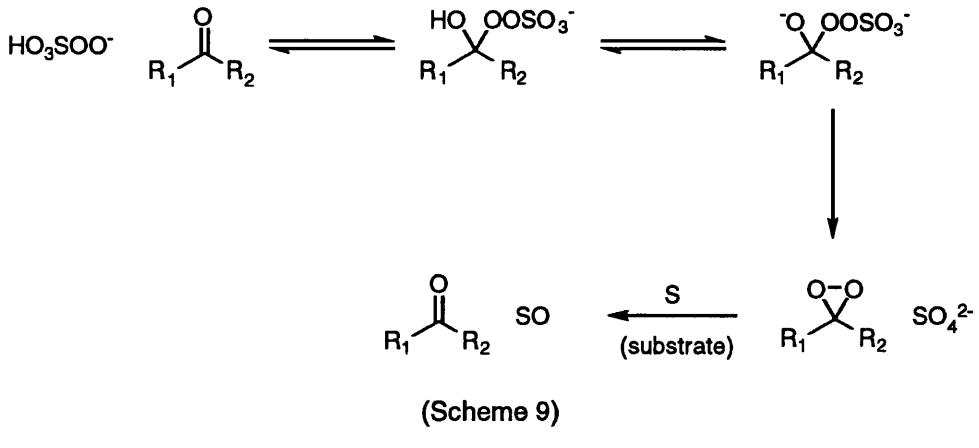
† caroate, HSO_5^-, is the mono anion of Caro's acid, H_2SO_5. Commercially available Oxone® is a triple salt $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$.

to achieve this acceleration, indicating that the role of the ketone was catalytic. Montgomery proposed a dioxirane as an intermediate but stopped short of saying that this species was responsible for chloride oxidation.

An important experiment that helped prove the existence of dioxiranes was carried out by Curci and Edwards. They used doubly ^{18}O labelled caroate and followed the path of the ^{18}O label.[12] Attack of this doubly labelled caroate on acetone should yield a dioxirane with 50% of the label in the caroate and the other 50% in the dioxirane. When a second equivalent of caroate attacks the dioxirane, then the oxygen produced should contain 75% of the ^{18}O label (Scheme 8). In fact, the oxygen produced was found to be labelled to an extent of 73 ±2%, giving powerful support to the intermediacy of dioxiranes in the ketone accelerated decomposition of caroate. Given this support for the intermediacy of dioxiranes, the mechanism in Scheme 9 was proposed for their formation and their oxidation of various substrates.



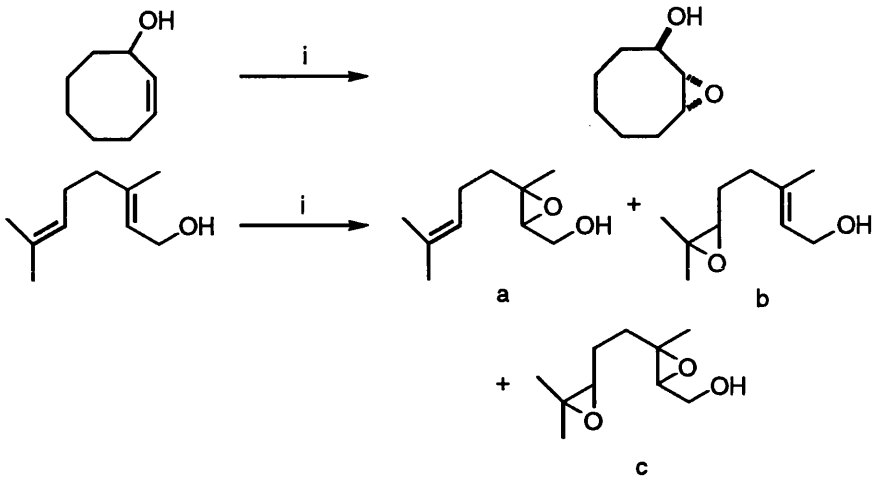
(Scheme 8)



(Scheme 9)

This evidence prompted Curci and co-workers to embark upon the epoxidation studies described earlier in this thesis.[5] In addition, they showed that this oxidising

system could be employed to epoxidise allylic alcohols stereo- and regioselectively (Scheme 10).[13]



Reagents and Conditions: (i), acetone, Oxone®, 18-crown-6, CH_2Cl_2, water, pH 7.5

(Scheme 10)

The main drawback in this method of epoxidation is the need for constant monitoring of the reaction and precise pH control. The need for constant pH control arises from the formation of HSO_4^- during the course of the reaction, which causes the pH of the mixture to fall. The control of pH was normally achieved by pH-stat. addition of KOH to the reaction mixture. The problem of constant pH control was later overcome by the use of $NaHCO_3$ as a buffer.[14] When excess $NaHCO_3$ was added to the reaction at the start and the Oxone® solution was added dropwise, the pH was found to remain within the limits needed for the reaction.

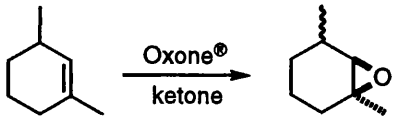
Since this work in the early to mid-1980s, many groups have used variations on these oxidising conditions to epoxidise alkenes. Ford showed that a $NaHCO_3$ buffered aqueous solution of Oxone® was capable of epoxidising alkenes in the absence of acetone and organic solvent (Table 1).[15] This is presumably due to direct electrophilic attack of the Oxone® on the alkene.

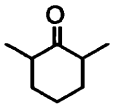
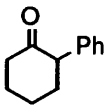
alkene	initial pH	final pH	epoxide (%)
cyclohexene	6.75	8.16	95
2,3-dimethyl-2-butene[a]	6.68	8.20	98
1-methylcyclohexene	6.68	7.60	91
α-methylstyrene[b]	7.05	7.18	33
styrene[c]	6.80	7.70	44
tetrachloroethylene	6.68	7.80	0

Reactions were performed at 23°C for 5 hrs with 0.35 mmol of alkene, 0.87 mmol of $NaHCO_3$ in 12 cm^3 of aqueous mixture and 0.44 mmol of $KHSO_5$ in 2.3 cm^3 of aqueous mixture. a) 0.7 mmol of alkene and 0.88 mmol of $KHSO_5$ in 4.6 cm^3 for 1 hr. b) 1.4 mmol of alkene, 2.4 mmol of $KHSO_5$ and 4.08 mmol of $NaHCO_3$ in 48 cm^3 of aqueous mixture. c) 0.6 mmol of $KHSO_5$ and 0.87 mmol of $NaHCO_3$ in 12 cm^3 of aqueous mixture.

(Table 1: Epoxidation of alkenes under the Ford Conditions)

Kurihara and co-workers studied the oxidation of 1,3-dimethyl-1-cyclohexene with a range of cyclohexanone derived ketones in a CH_2Cl_2 / MeOH / H_2O medium.[16] The problem with this system was its sizable background epoxidation (~30%) in the absence of ketone over the reaction time (Table 2). They also studied the epoxidation of cyclohex-2-en-1-ol under the same conditions. In both of the above cases the *anti* epoxide predominated with all ketones.

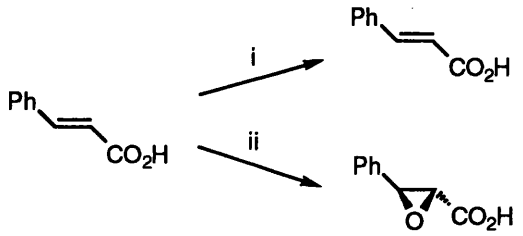


ketone	reaction time (hrs)	conversion (%)	*syn / anti*
acetone	3	56	14:86
cyclohexanone	3.5	80	9:91
	3.5	83	12:88
	4	68	7:93
none	2.5	28	25:75

Oxone® (5 mmol) in water added drop wise to a mixture of CH_2Cl_2 (2.5 cm^3), MeOH (20 cm^3) and buffered water (6 cm^3, pH 11.0, 0.5M phosphate buffer) containing alkene (0.5 mmol), ketone (5 mmol) and 18-crown-6 at 0°C.

(Table 2: Epoxidation Studies using the Kurihara System)

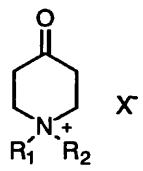
Acetonitrile / water mixtures have also been used as solvents for the *in situ* ketone / caroate epoxidation.[17] In this case the reaction medium is homogeneous, not a biphase, and a phase transfer reagent is not required. There has been a recent report of asymmetric epoxidation using a chiral, enantiomerically pure ketone.[18] However, only alkenes that possess electron poor double bonds were studied. This was presumably due to their low reactivity towards Oxone®, since in any homogeneous system, electron rich alkenes undergo direct and rapid epoxidation by Oxone®.[15, 19] This lack of reactivity towards Oxone® of electron deficient alkenes was demonstrated by Curci in his original paper (Scheme 11).[5] Cinnamates were found to be inert towards epoxidation by Oxone® in the absence of acetone.



Reagents and Conditions: (i), Oxone®, $EDTANa_2$, 1M NaOH, Phosphate buffer pH 7.2; (ii), as (i) but with acetone.

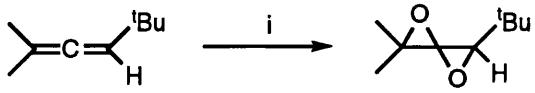
(Scheme 11)

Probably the most comprehensive study of the *in situ*, biphasic system was reported by Denmark.[20] He conducted a detailed study of the stoichiometries of Oxone®, ketone and phase transfer catalyst, as well as ketone structure and rates of caroate addition. He found that the best ketones for the reaction had structures of the type shown in Figure 1. To date these ketones are the most efficient promoters of the *in situ* reaction. A more comprehensive discussion on Denmark's findings will be presented in Chapter 4.



(Figure 1)

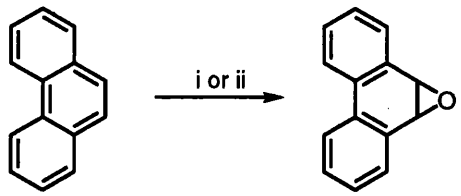
The proof that dioxiranes exist came with the isolation of DMDO as a solution in its parent ketone (acetone) in 1985.[21] Typical concentrations of DMDO ranged from 0.04-0.185M. These solutions may be dried using anhydrous K_2CO_3 and stored at -20 °C for up to a month with no loss of oxidising ability. Since its isolation, DMDO has proved to be an extremely powerful, neutral, selective and anhydrous reagent for the epoxidation of alkenes. It has been used to prepare acid sensitive epoxides, which are destroyed under standard peracid conditions[22] (for an example see Scheme 12).



Reagents and Conditions: (i), DMDO, acetone.

(Scheme 12)

DMDO has been shown to epoxidise alkenes in a stereospecific manner. Thus, on treatment with DMDO, *cis* alkenes yield *cis* epoxides exclusively. One of the great advantages of using isolated DMDO solution is that the work-up simply involves the removal of the solvent (normally acetone) by rotary evaporator. Since the initial isolation of DMDO, many other dioxiranes have been isolated in solutions of their volatile parent ketone.[23] One notable example is trifluoromethyl dioxirane (TMDO),[24] which has found widespread use due to its greater reactivity in oxidation processes than DMDO (Scheme 13).[24]



Reagents and Conditions: (i), DMDO, 25 °C, 45 mins, 83%;
(ii), TMDO, -20 °C, 5 mins, 93%.

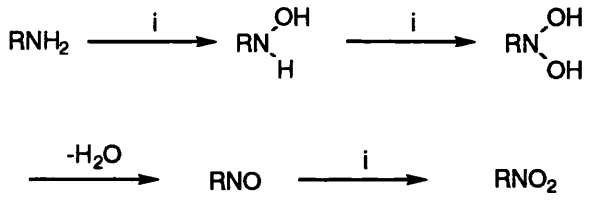
(Scheme 13)

1.2i: Dioxirane Oxidation of Compounds other than Alkenes

DMDO has been used to oxidise saturated hydrocarbons and compounds containing heteroatoms such as sulfur and nitrogen.

1.2ia: Nitrogen containing compounds

Primary amines are oxidised rapidly and in quantitative yields to nitro compounds.[25, 26] The oxidation is believed to proceed *via* a succession of O atom transfers. This is supported by the observation that phenylhydroxylamine and nitrosobenzene can be separately oxidised to nitrobenzene (Scheme 14). Secondary amines are converted to hydroxylamines and tertiary amines yield N-oxides when treated with DMDO.



Reagents and Conditions: (i), DMDO, acetone.

(Scheme 14)

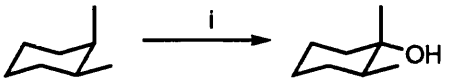
1.2ib: Sulfur containing compounds

Upon treatment with one equivalent of DMDO, sulfides are converted cleanly to the corresponding sulfoxide.[27] When a sulfoxide is treated with DMDO the expected sulfone results.[27]

1.2ic: Saturated Hydrocarbons

Perhaps the most surprising reaction of DMDO is its ability to oxidise saturated hydrocarbons[24] to either an alcohol or a ketone product. With suitable substrates this oxidation is found to be stereospecific, proceeding with retention of configuration

(Scheme 15).[28] In the oxidation of *n*-decane,[28] 2-decanone is the major product, 3-decanone and other compounds accounting for only 10% of the products observed. It seems that DMDO is sensitive to the most subtle of electronic effects in such hydrocarbons.



Reagents and Conditions: (i), DMDO, acetone.

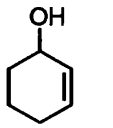
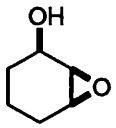
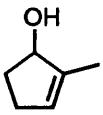
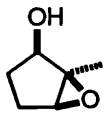
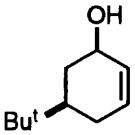
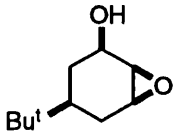
(Scheme 15)

1.3: Directed Epoxidation Reactions

A review of directed epoxidation reactions, including those by DMDO, will be presented in this section. This discussion will only be brief since Evans, Hoveyda and Fu have written an excellent article on the subject of directed reactions recently.[1]

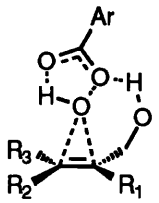
1.3i: Hydroxyl Directed Peracid Epoxidation

In 1959, Henbest and Wilson showed that peracid epoxidation of allylic alcohols within a steroid occurred *cis* to the hydroxyl group.[29] This overrode the intrinsic steric bias of the conformationally well defined steroid skeleton. This selectivity was also shown to be in effect in the peracid epoxidation of simple cyclic allylic alcohols (Table 3).

Substrate	Major Product	Selectivity
		10:1
		>20:1
		24:1

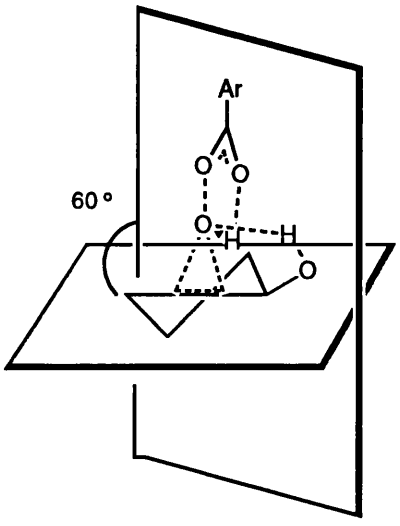
(Table 3: Stereoselective Epoxidation of Cyclic Allylic Alcohols with *m*CPBA)

When the hydroxyl group was protected as either an ester or an ether then the reaction was found to yield predominantly the *anti*-isomer.[29, 30] The stereochemical outcome of the reaction was rationalised by Bartlett,[31] as involving a butterfly type mechanism where there is an additional interaction between the allylic alcohol of the nucleophilic alkene and the electrophilic peracid. This was thought to involve hydrogen bond formation between the hydroxyl proton and the centre peracid oxygen, leading to delivery of oxygen to the face of the alkene *syn* to the hydroxyl group (Figure 2).



(Figure 2)

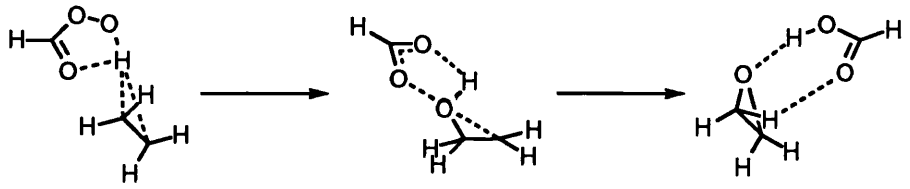
Sharpless, however, has proposed that a dihedral angle of 60° exists between the planes defined by the two molecules (Figure 3).[32] This would position one of the non-bonding electron pairs of the peracid for donation into the π^* C=C orbital, thus initiating formation of the second C-O bond of the epoxide. This orientation also puts the other non-bonding lone pair of the terminal peracid oxygen in a good position to hydrogen bond with the hydroxyl on the alkene. This is an unsymmetrical transition structure as opposed to Bartlett's symmetrical one. Molecular modeling suggests that the symmetrical case would position the hydroxyl proton and the peracid oxygen too far away to form hydrogen bonds, but in an unsymmetrical transition state these atoms would be close enough together to interact.[32] The main difference between the Sharpless and Bartlett models is that Sharpless reasons that for the necessary stereoelectronic requirements to be fulfilled, hydrogen bonding occurs to the terminal oxygen in the peracid and not the centre one as suggested by Bartlett.



(Figure 3)

Although there is no experimental or theoretical evidence to distinguish between the two proposed models, the role of hydrogen bonding has been established. It has been noted in some systems that when the solvent for the reaction is changed from either ether or CH_2Cl_2 to methanol then the *anti* epoxide predominates.[30] This is presumably due to methanol competing with the peracid for the formation of hydrogen bonds to the allylic alcohol. Regardless of the solvent used in the epoxidation of the corresponding allylic methyl ether, the ratio of epoxide products remains unchanged and favours the *anti* isomer.[30]

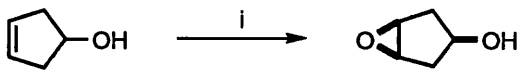
Recently a series of calculations by Yamabe suggested that the peracid epoxidation of alkenes is not a concerted process.[33] Yamabe proposed that one C-O bond of the epoxide is formed first generating an unsymmetrical intermediate (Scheme 16, **B**). This intermediate is thought to be unstable and transient, rapidly closing to the epoxide before rotation of the intermediate's C-C bond can occur (Scheme 16).



A **B** **C**

(Scheme 16)

Cyclic homoallylic alcohols have also been shown to direct peracid epoxidations[1, 30] to yield *syn* epoxides as the major products (Scheme 17). Bishomoallylic cyclic alcohols however, have little or no influence on the outcome of peracid epoxidation.

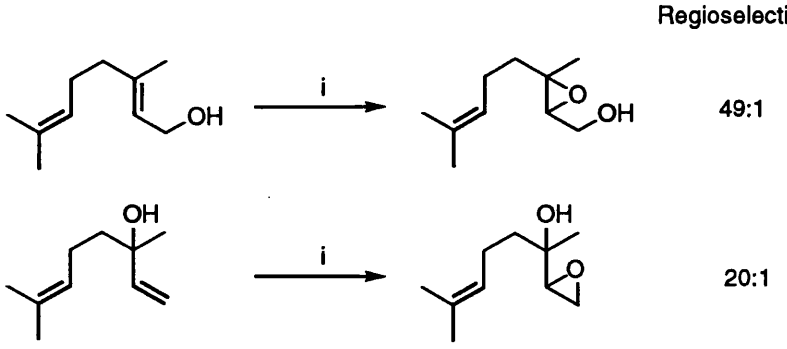


Reagents and Conditions: (i), *m*CPBA, Et_2O.

(Scheme 17)

1.3ii: Hydroxyl Directed Metal Catalysed Epoxidation

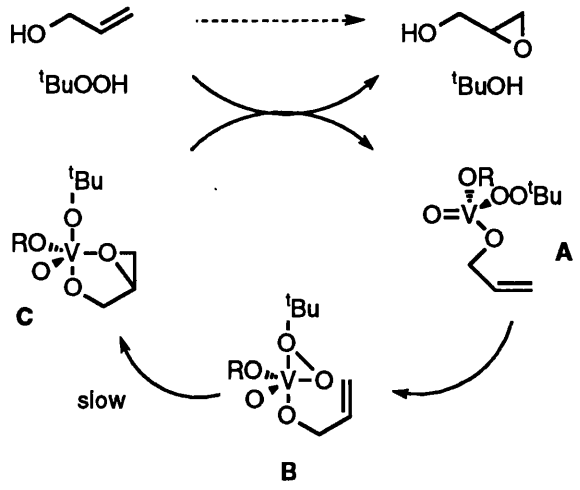
In the late 1960's it was found that TBHP could be used to epoxidise alkenes in the presence of a transition metal catalyst,[34] containing an element such as titanium, vanadium or molybdenum. It was noted that these reactions proceeded at a vastly accelerated rate when the substrate contained a hydroxyl group[35] in an allylic, homoallylic or bishomoallylic position. This acceleration was by far the greatest when vanadium was employed as the metal in the catalyst. The epoxidation was found to be regioselective,[36] such that if multiple carbon - carbon double bonds were present then the double bond closest to the hydroxyl group would be epoxidised (Scheme 18). This is in contrast to the peracid epoxidation of geraniol and linalool, which are epoxidised at the double bond furthest from the hydroxyl group.



Reagents and Conditions: (i), TBHP, $VO(acac)_2$, CH_2Cl_2.

(Scheme 18)

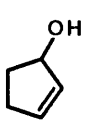
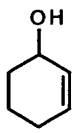
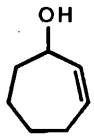
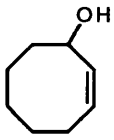
As well as being regioselective, the metal catalysed epoxidation showed excellent *syn* selectivity in cyclic alkenes with hydroxyl groups present. This is consistent with intramolecular delivery of oxygen. Although the mechanism of these epoxidations is not clear, Sharpless has proposed that the vanadium catalysed reaction proceeds *via* the cycle in Scheme 19.[32] The $VO(acac)_2$ is oxidised by the TBHP to a catalytic d^0 vanadate ester complex, which undergoes rapid ligand exchange to give **A**. The alkyl peroxide is activated by bidentate cyclic co-ordination to give **B**. Nucleophilic attack by the alkene now takes place in the rate- and stereochemical determining step to yield **C**.



(Scheme 19)

1.3iia: Cyclic Allylic Alcohols

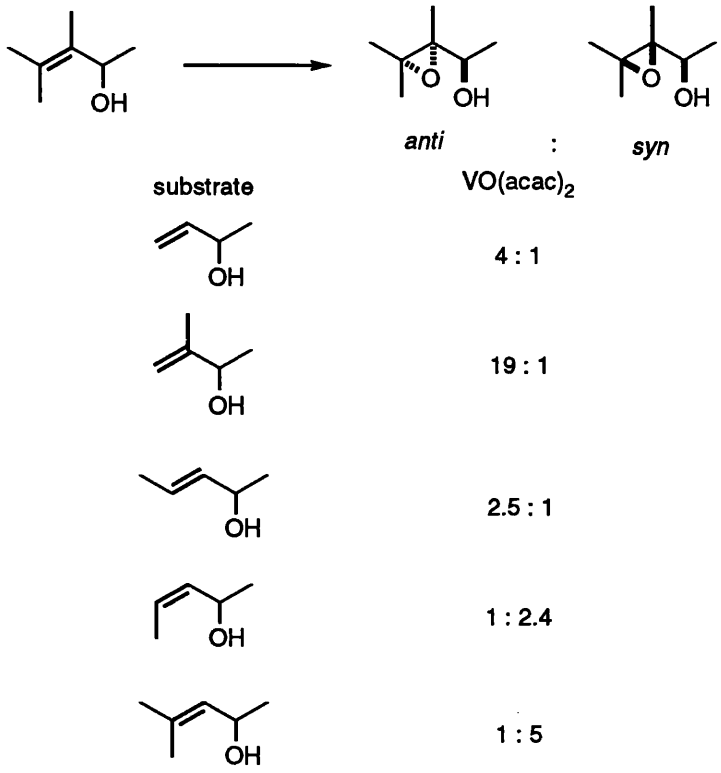
As suggested above, vanadium catalysed TBHP epoxidations of cyclic allylic alkenes occur *syn* to the hydroxyl group[37, 38] for all ring sizes (5-9). This is in contrast to peracid epoxidation which occurs predominantly *anti* for medium ring sizes (7-9). A summary of $VO(acac)_2$ / TBHP epoxidation selectivities is shown in Table 4.

substrate				
$VO(acac)_2$ / TBHP selectivity *syn* : *anti*	99.2 : 0.8	99.7 : 0.3	99.6 : 0.4	97 : 3

(Table 4: Stereoselectivity in the $VO(acac)_2$ / TBHP Epoxidation of Cyclic Allylic Alcohols)

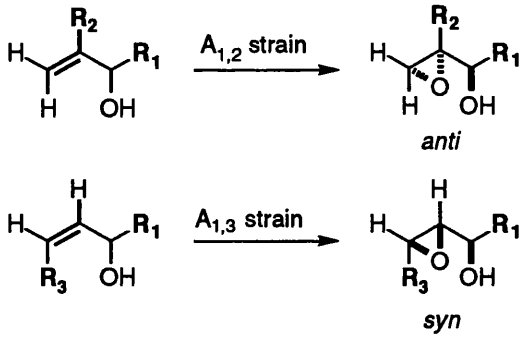
1.3iib: Acyclic Allylic Alcohols

Sharpless showed that acyclic allylic alcohols could be epoxidised with a high degree of diastereoselectivity using the $VO(acac)_2$ / TBHP system.[39] He concluded that the highly ordered transition state proposed by his mechanism is responsible for the high degree of diastereoselectivity observed (Table 5).



(Table 5: Epoxidation Selectivity of Acyclic Allylic Alcohols)

The factors that dominate the stereochemical outcome of the reaction are steric and stereoelectronic in nature. The main ones are (i) $A_{1,2}$ strain, (ii) $A_{1,3}$ strain, (iii) interactions between ligands on vanadium and a R group on the substrate and (iv) hyperconjugative donation into the π^* orbital on the alkene. It is, however, minimisation of allylic strain[40] (Scheme 20) that plays the deciding role. Only in the absence of any significant strain do the stereoelectronic requirements become important.

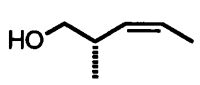
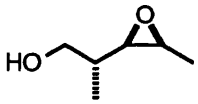
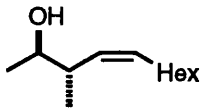
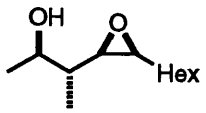
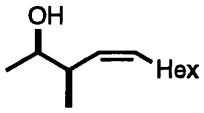
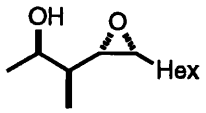
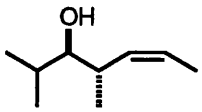
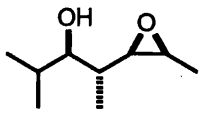
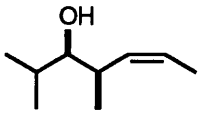
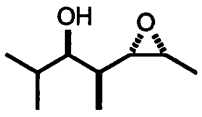


(Scheme 20)

The *anti* selectivity for the cases exhibiting $A_{1,2}$ lock increases with the increase in size of the R_1 and / or R_2 groups. Under the same conditions, increasing the size of the R_1 and / or R_3 groups in the cases where $A_{1,3}$ strain dominates, increases the *syn* selectivity of the reaction. A further discussion on the nature of $A_{1,3}$ strain will be presented later in this thesis in the section that deals with the epoxidation of acyclic keto-alkenes. It is worthy of mention that Sharpless' extensive and detailed work on metal catalysed allylic epoxidation reactions led to the discovery of the $Ti(O^iPr)_4$ / diethyl tartrate asymmetric epoxidation.[41]

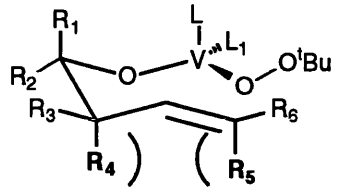
1.3iic: Acyclic Homoallylic Alcohols

It was found that homoallylic alcohols could also direct the course of the $VO(acac)_2$ / TBHP epoxidation, and in the early 1980's Michelich performed an extensive and comprehensive study on the diastereoselectivity of this reaction (Table 6).[42]

	Substrate	Major product	Selectivity
1			>400:1
2			104:1
3			70:1
4			>400:1
5			2.1:1

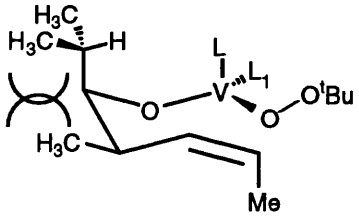
(Table 6: Epoxidation Selectivities in Homoallylic Alcohols)

It was proposed that the face of the alkene to be attacked and the magnitude of the diastereoselectivity could be predicted by analysis of a chair-like transition state structure (Figure 4).



(Figure 4)

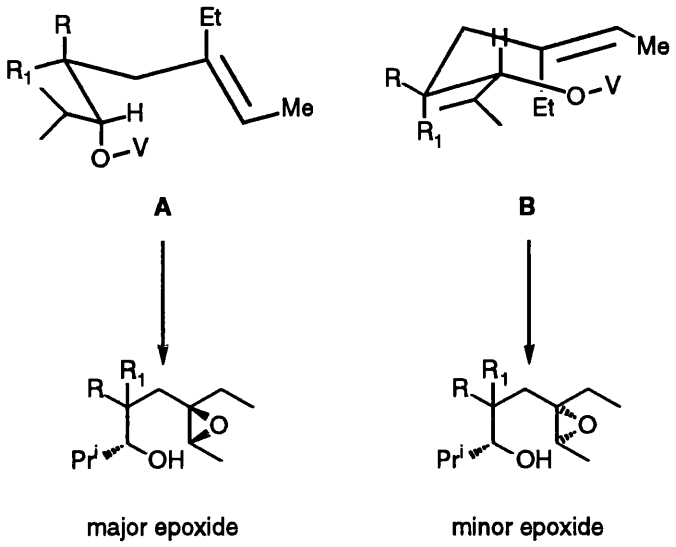
All the results in Table 6 can be rationalised by the above structure (Figure 4), which minimises steric interactions among the different substituents according to the well known principles of conformational analysis. Entries 1, 2 and 4 (Table 6), have high selectivities as the favoured transition state has R_1= R_4= H with R_3 and R_5= alkyl. Formation of the minor isomer would require R_4= R_5= alkyl, which is highly disfavoured. In the case of entry 3, R_1= alkyl to avoid a severe R_4- R_5 interaction; selectivity is reduced and the reaction rate is also slowed. In entry 5, however, there is no chair conformation that is free of severe destabilising interaction, and so competition with the boat form leads to lower diastereoselectivity (Figure 5).



(Figure 5)

1.3iid: Acyclic Bishomoallylic Alcohols

Kishi first demonstrated that bishomoallylic alcohols could be used to direct the course of the $VO(acac)_2$ / TBHP epoxidation in his synthesis of lasalocid A.[43,44] He also helped to elucidate the necessary requirements for good stereocontrol (Figure 6).



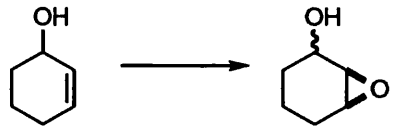
(Figure 6)

Two transition structures were proposed by Kishi. Structure **A** is indicated by modeling to be the most favoured as it minimises transannular compression between the R_1 and the Et groups present in structure **B**. This explains the sense of the facial selectivity in the bishomoallylic system.

Other catalysts based on metals such as tungsten,[45] aluminium[46] and tin[47] have also been used to direct the course of epoxidation in allylic alcohols, but as yet no comprehensive study of their selectivity and reactivity has been reported.

1.3iii: Hydroxyl Directed DMDO Epoxidation

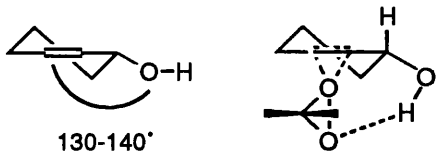
The hydroxyl group of substituted cyclohex-2-en-1-ols has recently been shown to direct the course of DMDO epoxidations.[48, 49] It was shown that this directing effect was strongly influenced by the nature of the solvent in the reaction. If DMDO in acetone was used then both epoxides were formed in nearly equal amounts, with a slight preference for the *anti* isomer. This favouring of the *anti* epoxide increased as the DMDO / acetone mixture was diluted with methanol. Conversely, if the DMDO / acetone solution was diluted with either CH_2Cl_2 or CCl_4 then the *syn* epoxide was found to predominate (Table 7).



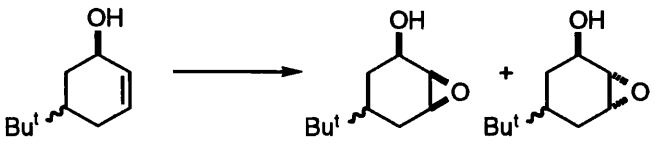
Solvent System	Epoxide ratio Epoxide ratio *syn / anti*
acetone	46:54
1:1 CH_2Cl_2 / acetone	57:43
9:1 CH_2Cl_2 / acetone	78:22
97:3 CH_2Cl_2 / acetone	82:18
9:1 MeOH / acetone	34:66
9:1 CCl_4 / acetone	85:15
20:1 CCl_4 / acetone	94:6

(Table 7: Solvent Effect on the DMDO Epoxidation of cyclohex-2-en-1-ol)

This trend was attributed to the dioxirane forming a hydrogen bond to the hydroxyl group in the allylic alcohol. In the CCl_4 / acetone system, the presence of CCl_4 must weaken the association between the dioxirane and acetone so that hydrogen bonding of the dioxirane to the substrate hydroxyl is more competitive. In the methanol / acetone system there is less opportunity for substrate - reagent hydrogen bonding, so the *anti* epoxide product predominates. Adam and Smerz[49] proposed that a dihedral angle of about 130-140° (Figure 7) was optimum for the hydroxyl group to direct DMDO epoxidations. This was based on AM1 calculations and experimental observation in the epoxidation of *cis* and *trans* 5-*tert*butylcyclohex-2-en-1-ol in a variety of DMDO / acetone / co-solvent systems (Table 8).[49] Comparison of entries 3 and 6, Table 8, performed in a non-polar solvent, showed that the hydroxyl group of *cis* 5-*tert*butylcyclohex-2-en-1-ol could direct the epoxidation to a greater extent than the corresponding hydroxyl group in *trans* 5-*tert*butylcyclohex-2-en-1-ol.



(Figure 7)



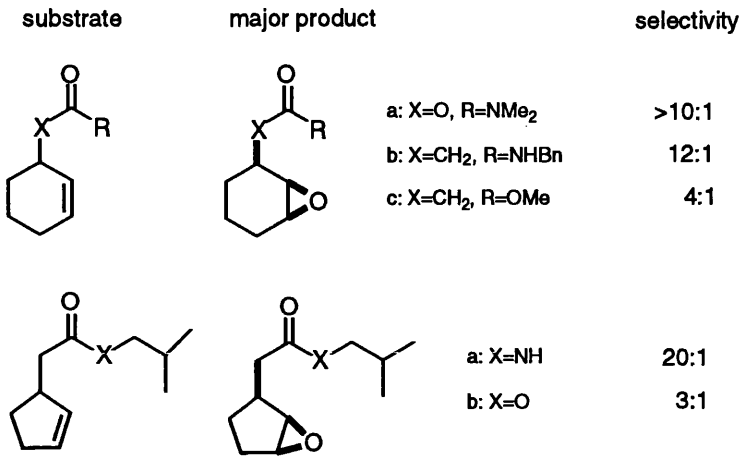
Entry	Substrate	Solvent	Epoxide product *syn / anti*
1	*trans*	9:1 MeOH/ acetone	29:71
2	*trans*	acetone	30:70
3	*trans*	9:1 CCl_4/ acetone	58:42
4	*cis*	9:1 MeOH/ acetone	38:62
5	*cis*	acetone	60:40
6	*cis*	9:1 CCl_4/ acetone	82:18

(Table 8: Solvent Effect on the DMDO Epoxidation of 4-*tert*butylcyclohex-2-en-1-ol)

For both allylic alcohols, steric factors control the epoxidation in the methanol / acetone system (entries 1 and 4, Table 8), leading to predominance of the *anti* isomer. *Syn* selectivity is observed when a less polar solvent system is used. In these systems, the *trans* allylic alcohol's hydroxyl group is not sufficiently well aligned to achieve high diastereoselectivity. When cyclohex-2-en-3, 5, 5-trimethyl-1-ol (the dihedral angle of which was calculated to be 137.1°) was epoxidised under DMDO / acetone / CCl_4 conditions, the ratio of *syn* to *anti* epoxides was found to be 96:4. This ratio is comparable to the selectivities seen in the peracid directed epoxidations discussed earlier.

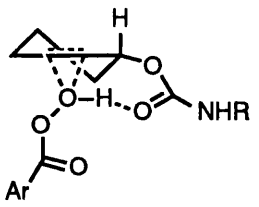
1.3iv: Carbonyl Directed Peracid Epoxidation

Carbonyl groups have been shown to direct the course of peracid epoxidations. It has been shown that allylic carbamates and homoallylic carbamates, esters and amides can direct peracid epoxidation with varying degrees of success.[50-52] The degree of influence exerted by the carbonyl group over the epoxidation reaction was shown to be related to the type of carbonyl group present in the molecule. The more Lewis basic the carbonyl group, the better able that carbonyl group is to form a hydrogen bond to the peracid's hydroxyl proton. This is illustrated in Table 9, where it can be seen that carbamates and amides react with a higher degree of selectivity than esters.



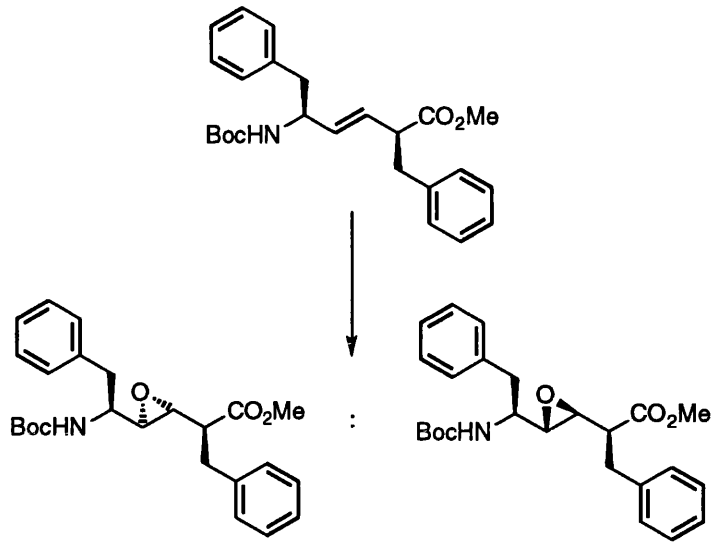
(Table 9: Selectivities in Carbonyl Directed Peracid Epoxidations)

A transition state structure has been proposed (Figure 8).[50b] In this, the oxygen of the carbonyl group forms an intermolecular hydrogen bond with the acidic proton of the peracid. This directs delivery of oxygen to the face of the alkene *syn* to the carbonyl group. This proposed hydrogen bonding scheme is effectively the reverse of the hydroxyl directed peracid epoxidation, in which the hydroxyl proton of the allylic alcohol is proposed to form a hydrogen bond to the terminal peracid oxygen.



(Figure 8)

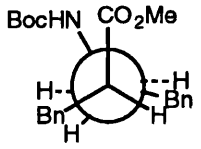
In a recent report, Luthman[52] showed that Phe-Phe and Phe-Gly vinyl isosteres could direct the course of the peracid epoxidation to a particular face of the double bond (Scheme 21).



9 : 1

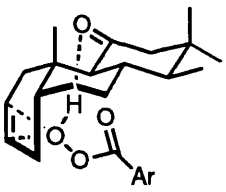
(Scheme 21)

This was rationalised by the formation of two co-operative hydrogen bonds between the carbamate and peracid and the ester and peracid. For this to occur the molecule must adopt a conformation where the two hydrogen bonding groups are virtually eclipsing each other (Figure 9).



(Figure 9)

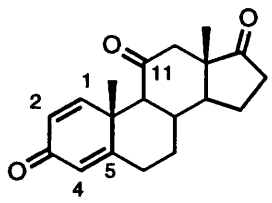
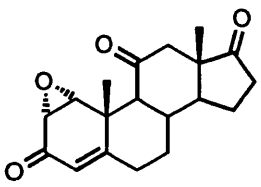
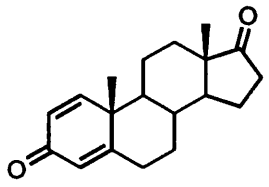
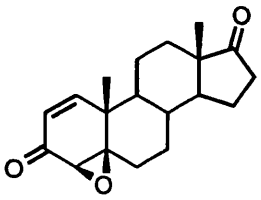
Ketone carbonyl groups contained within a rigid, well defined system have also been suggested to exert a directing effect on peracid epoxidation.[53] One of the first examples of this effect was concerned with 11-keto, 25-D, 5β spirost-2-ene series of steroids. In unsubstituted steroids of this type, addition of reagent occurs from the less hindered β-face. When a ketone group was introduced at C-11, this selectivity was found to be reversed. This reversal of selectivity was explained by hydrogen bonding between the carbonyl and the peracid (Figure 10). Indeed, in accordance with this theory, when acetonitrile was used as a solvent instead of hexane a decrease in the selectivity of the reaction was observed.



(Figure 10)

1.3v: Carbonyl Directed DMDO Epoxidation

There is to date one example in the literature of a ketone carbonyl group being able to influence the course of DMDO epoxidation (Table 10).[54]

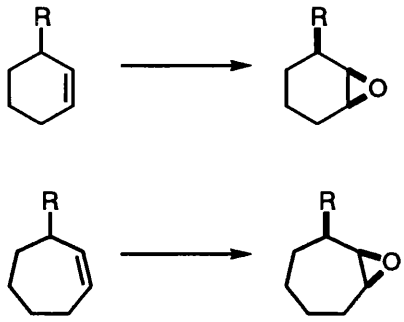
Substrate	Major product	Selectivity
		1α-2α: 80% 4β-5β: 15% 4α-5α: 5%
		4β-5β: 81% 4α-5α: 12% 1α-2α: 6% 1β-2β: 1%

(Table 10: Selectivity in the DMDO Epoxidation of steroidal 1, 4 dien-3-ones)

In these cases, the C-11 carbonyl directed the epoxidation to what is usually considered the less reactive 1,2-double bond. When the C-11 carbonyl was removed, epoxidation was found to favour attack on the 4,5-alkene from the less hindered β-face. This regioselectivity was explained in terms of the tendency of the dipoles of the carbonyl and dioxirane to be in opposition in order to minimise the overall dipole moment.

1.3vi: Carbonyl Directed Metal Catalysed Epoxidation

In studies directed towards a general synthesis of the trichothecenes, Pearson found that ester functionality could direct the course of $Mo(CO)_6$ / TBHP epoxidation[55] to a greater degree than that exhibited by *m*CPBA (Table 11).



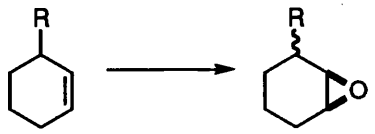
	Selectivity *syn / anti*	
R	*m*CPBA	$Mo(CO)_6$
CH_2CO_2Me	4:1	15:1
OAc	1:1.5	*syn* only
CH_2CO_2Me	1:1.2	1:2
OAc	1.6:1	5.2:1

(Table 11: Selectivities in the $Mo(CO)_6$ Catalysed Epoxidation)

As can be seen in the above Table, allylic acetates are shown to direct the course of epoxidation with significant effect. These results are in contrast to epoxidation with peracids or $VO(acac)_2$, where acylation of cyclic allylic alcohols leads to loss of the stereo-directing effect. Pearson provided no explanation for his observations.

1.3vii: Other Directed DMDO Epoxidation Reactions

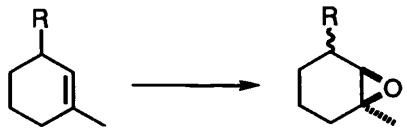
Murray has recently published a study of the directing effect of different functional groups on the DMDO epoxidation[56] of three types of substituted cyclic alkenes in solvents of different polarity (Tables 12, 13 and 14).



Entry	R	Solvent	Ratio *anti* / *syn*
1	NHCOPh	acetone	19:81
		9:1 CCl_4 / acetone	3:97
		9:1 MeOH / acetone	26:74
2	CF_3	acetone	90:10
		1:1 CH_2Cl_2 / acetone	94:6
3	CN	acetone	51:49
		1:1 CH_2Cl_2 / acetone	57:43
4	Me	acetone	48:52
		9:1 CH_2Cl_2 / acetone	53:47
5	^tBu	acetone	95:5
		9:1 CH_2Cl_2 / acetone	96:4
6	CO_2H	acetone	84:16
		$CHCl_3$ / acetone	87:13

(Table 12: Diastereoselectivities in the DMDO Epoxidation of cyclohex-2-en-1-ol derivatives)

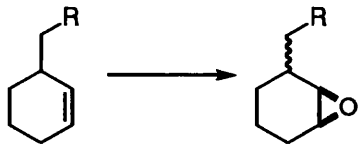
As can be seen from Table 12, the epoxidation of cyclohexene bearing an amide substituent (entry 1) occurred with *syn* selectivity. This selectivity increased as the solvent used became less polar. This result suggested that the formation of a hydrogen bond between the amide and DMDO played an important part in the selectivity. Methyl and nitrile substituents (entries 3 and 4, Table 12) were effectively unselective. Carboxylic acid, trifluoromethyl and *tert*-butyl substituents (entries 2, 5 and 6, Table 12) all showed *anti* selectivity and were unaffected by a change in solvent. The *anti* selectivity was rationalised by invoking an argument based on steric hindrance.



Entry	R	Solvent	Ratio *anti / syn*
1	OH	acetone	65:35
		9:1 MeOH / acetone	82:18
		9:1 CCl_4 / acetone	21:79
2	OMe	acetone	95:5
		95:5 CCl_4 / acetone	5:95
3	OCOMe	acetone	87:13
		9:1 CCl_4 / acetone	88:12
4	CH_3	acetone	73:27

(Table 13: Diastereoselectivities in the DMDO Epoxidation of 3-methylcyclohex-2-en-1-ol derivatives)

The results presented in Table 13 show that for hydroxyl and methoxy bearing substrates (entries 1 and 2) the *syn* selectivity increased with a decrease in solvent polarity. This was attributed to hydrogen bond formation and a dipole interaction for entries 1 and 2 respectively. Systems containing an acetate or a methyl group (entries 3 and 4, Table 13) showed *anti* selectivity which was not dependent upon the solvent polarity.



Entry	R	Solvent	Ratio *anti / syn*
1	OH	acetone	44:56
		9:1 MeOH / acetone	55:45
		95:5 CCl_4 / acetone	26:74
2	Br	acetone	38:62
		9:1 CCl_4 / acetone	27:73
3	OCOMe	acetone	40:60
4	CO_2Et	acetone	25:65
		9:1 CCl4 / acetone	27:73
		9:1 MeOH / acetone	41:59

(Table 14: Diastereoselectivities in the DMDO Epoxidation of Homoallylic cyclohexenes)

In the homoallylic series (Table 14) all substrates showed some measure of *syn* selectivity. This selectivity increased with a decrease in solvent polarity. In the case of the homoallylic alcohol (entry 1, Table 14) this selectivity was rationalised by hydrogen bond formation. In the cases of the bromide, acetate and ethyl ester (entries 2, 3, and 4, Table 14) the selectivity was explained by an interaction between the dipoles of the substrate and DMDO.

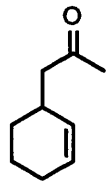
In summary, the results in the above Tables were rationalised in terms of three factors. The first of these, and the factor that exerts the greatest influence on the epoxidation, was a hydrogen bonding effect between the substrate and DMDO (entry 1, Table 12, entry 1, Table 13 and entry 1, Table 14). This presumably only operates when there is an acidic proton in the molecule for DMDO to form a hydrogen bond to. This has been described in an earlier section of this thesis. The second of these factors was a dipole - dipole alignment between the substrate and DMDO. Although the effect of this on the epoxidation is not as great as the effect of hydrogen bonding, this is especially relevant in the homoallylic series (entries 2, 3, and 4, Table 14) where, in the majority of cases, a hydrogen bonding mechanism is impossible due to the lack of an acidic proton in the alkene. As can be seen the *syn / anti* ratio increases when the solvent is diluted with carbon tetrachloride, reducing solvent polarity and thus enabling a dipole - dipole interaction between the substrate and DMDO to influence the epoxidation. This interaction is disrupted by the presence of methanol. In the examples studied that do not contain groups that can either form hydrogen bonds to, or have a strong dipole - dipole interaction with DMDO (entries 2-6, Table 12 and entries 3 and 4, Table 13) steric effects dominate. In the case of cyclohex-2-en-1-ol derivatives, the *anti / syn* ratio increases with the size of the alkyl group present (entries 3-5, Table 12).

Chapter 2:

Peracid Epoxidation of Cyclic Keto-Alkenes

2.1: Results and Discussion

As an initial candidate for our investigations into ketone directed epoxidation, it was decided to synthesise keto-alkene **1** (Figure 11). It was considered that any intramolecular epoxidation process would yield exclusively the *syn* epoxide isomer. The *anti* isomer could not be formed as it is geometrically impossible for the ketone tether to reach that face of the double bond. Intermolecular epoxidation would be expected to yield predominantly the *anti* isomer for simple steric reasons.

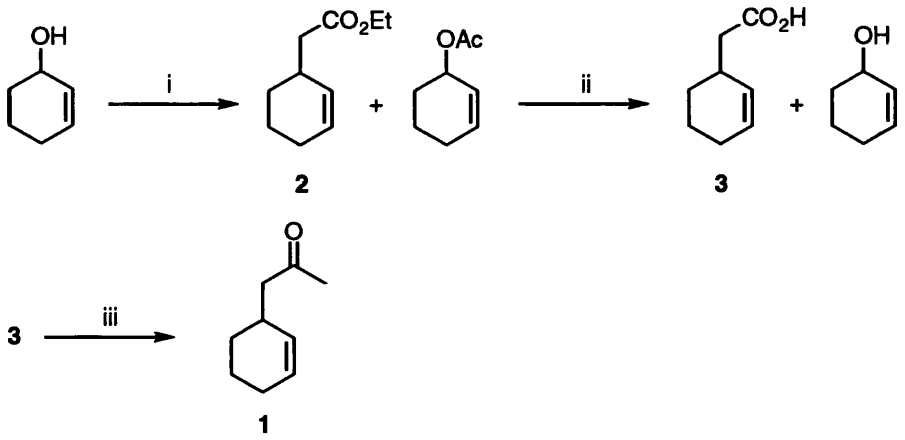


1

(Figure 11)

Keto-alkene **1** was synthesised according to the route outlined in Scheme 22. A Johnson orthoester variation of the Claisen rearrangement[57] on cyclohex-2-en-1-ol furnished a mixture of the desired ethyl ester **2** and the acetate of cyclohex-2-en-1-ol in roughly equal quantities. The acetate presumably arises from hydrolysis of the ketene acetal intermediate before rearrangement can occur. While Jones has reported conditions that obviate the undesired acetate formation,[58] the conditions used were suitable for the preparation of gram quantities of ester **2**. The esters proved to be inseparable by flash column chromatography, so the crude mixture was hydrolysed to yield the desired acid **3** and cyclohex-2-en-1-ol, which were then separated by standard acid / base manipulations. The acid was converted into keto-alkene **1** by addition of MeLi according to the procedure of Rubottom.[59] This involved quenching the reaction with excess TMSCl to destroy any excess MeLi and to trap out the tetrahedral dianion intermediate. This ensures that the tetrahedral intermediate does not break down to form ketone, which could react further with MeLi to yield tertiary alcohol, before all the MeLi is quenched.

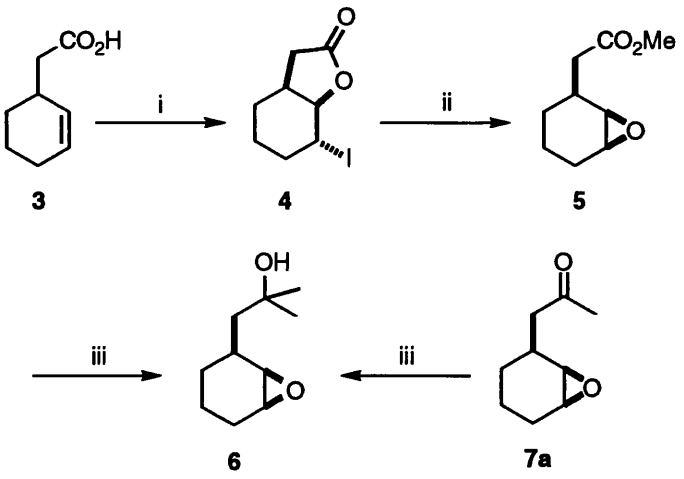
Yields of this reaction proved to be variable due in part to the volatility of keto-alkene **1**, but yields over 60% were regularly obtained.



Reagents and Conditions: (i), $CH_3C(OEt)_3$, $C_2H_5CO_2H$, 140°C; (ii), 1M NaOH, MeOH, 37% over two steps; (iii), MeLi, TMSCl, THF, 0°C, 85%.

(Scheme 22)

Keto-alkene **1** was epoxidised by *m*CPBA[60] in a CH_2Cl_2 / saturated aqueous sodium bicarbonate solution in an attempt to generate authentic isomers of *syn* and *anti* epoxides for spectroscopic comparison to any epoxides generated by intramolecular dioxirane epoxidation. It was surprising to discover that peracid epoxidation yielded only one epoxide isomer by ^1H and ^{13}C NMR. It was impossible to determine from the NMR spectra which isomer had been formed, so a series of correlation experiments was conducted (Scheme 23).



Reagents and Conditions: (i), I_2, MeCN, 34%; (ii), MeONa, MeOH, 57%; (iii), MeLi, THF, -78°C, 45%.

(Scheme 23)

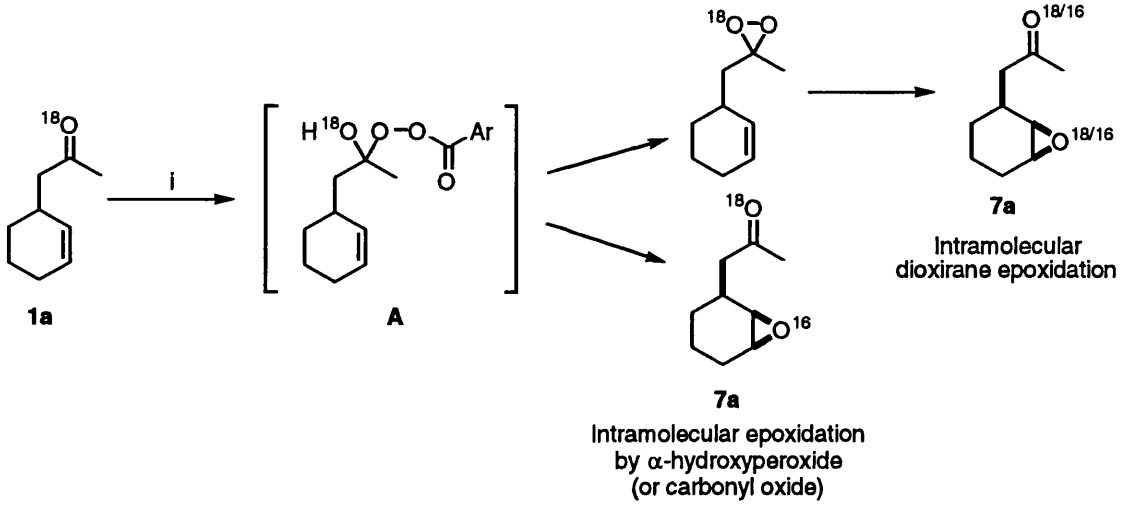
Treatment of acid **3** with iodine in acetonitrile provided iodolactone **4**. The iodolactone was opened with sodium methoxide solution to yield the known *syn* epoxy-ester **5**.[50b] The epoxy-ester was treated with MeLi to yield the tertiary *syn* epoxy-alcohol **6**. This compound is also the expected product of the reaction of MeLi with the *syn* keto-epoxide **7a**. Indeed, when the epoxide obtained by the reaction of keto-alkene **1** with *m*CPBA was treated with MeLi, it was found that the product was spectroscopically identical to the *syn* epoxy-alcohol **6**. Therefore, the sole product of the reaction of *m*CPBA and keto-alkene **1** is the *syn* keto-epoxide **7a**.

An obvious possible reason for the *syn* selectivity was hydrogen bonding. However, this would be surprising in light of the trend in the peracid epoxidation of carbonyl containing compounds from the work of Kocovsky[50] discussed earlier. As the carbonyl group became less Lewis basic it was less able to form a hydrogen bond to the peracid and thus directed the course of peracid epoxidation with lower *syn* selectivity. As the carbonyl group of a ketone is of comparable or smaller Lewis basicity than that of an ester, it would be expected that the *syn* selectivity of the epoxidation reaction would be smaller in the former case.

To test the role of hydrogen bonding, keto-alkene **1** was epoxidised by *m*CPBA in a variety of solvents[60] (CH_2Cl_2, ether, benzene, methanol and *tert*-butanol), and in all cases the only product formed was the *syn* keto-epoxide **7a**. This study tended to suggest that a hydrogen bonding mechanism was not responsible for the observed selectivity. If hydrogen bonding were responsible then the selectivity would be expected to decrease in solvents like methanol where competitive hydrogen bonding of the peracid to the solvent can occur.

Another interesting possibility is that the *m*CPBA undergoes addition to the ketone carbonyl group. This is the first step in the Baeyer-Villiger oxidation, a process that generally does not occur for simple acyclic aliphatic ketones like acetone upon treatment with *m*CPBA, due to the low migratory aptitude of primary alkyl groups. Acetone, however, has been shown to react with peracetic acid to produce a species capable of alkene epoxidation; this intermediate was postulated to be either a carbonyl oxide or a dioxirane.[61]

An ^{18}O labelling experiment was devised to test this interesting possibility of dioxirane formation. Assuming addition of *m*CPBA to the carbonyl group is stereo-random, then a resulting dioxirane would have the ^{18}O label distributed equally between its two diastereotopic oxygens. Epoxidation would then lead to a partitioning of the label between the carbonyl group and the epoxide (Scheme 24). A dioxirane intermediate could be formed without label transfer to the alkene only if addition to the carbonyl were stereoselective and the labelled oxygen was geometrically incapable of intramolecular epoxidation. This is unlikely, however, since molecular models suggest that either oxygen is geometrically capable of being transferred.

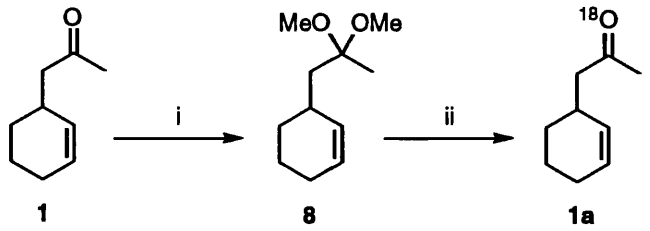


Reagents and Conditions: (i),*m*CPBA.

(Scheme 24)

The ^{18}O label was incorporated into keto-alkene **1** *via* conversion into to its dimethyl ketal by heating to reflux in methanol / 2,2-dimethoxy propane in the presence of catalytic *p*-toluenesulfonic acid. The ketal was hydrolysed with $H_2{}^{18}O$ to yield the labelled ketone **1a** (Scheme 25). Confirmation that the label was incorporated was obtained by mass spectrometry ($M^+ = 140$) and ^{13}C NMR. It is known that a carbon bonded to ^{18}O is shifted very slightly upfield with respect to its ^{16}O bonded position in the ^{13}C NMR spectrum.[62, 63] In the ^{13}C NMR of labelled **1a**, however, all peaks were very slightly shifted, which indicated that the NMR spectrum was concentration dependent. A mixed sample of labelled and unlabelled keto-alkene (**1a** and **1**) was run and this clearly showed

two carbonyl peaks at 207.91 and 207.85 ppm, confirming the presence of ^{18}O label in the sample.



Reagents and Conditions: (i), MeOH, $HC(OMe)_3$, cat. TsOH, 98%; (ii), $H_2{}^{18}O$, cat. H_2SO_4, THF, 76%.

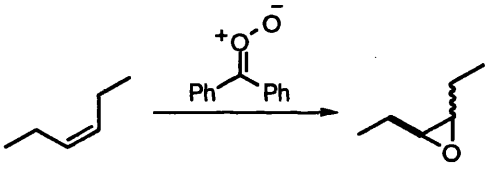
(Scheme 25)

The labelled keto-alkene **1a** was epoxidised with *m*CPBA in either CH_2Cl_2 / saturated aqueous $NaHCO_3$, or in ether. In both cases there was found (by ^{13}C NMR and MS) to be no evidence of doubling of the epoxide resonances at 55.1 and 53.5 ppm that would be expected for a $^{16/18}O$ label mixture. Typically the resonances would be shifted to a lower frequency by 0.03 to 0.04 ppm for an epoxide.[63] Two carbonyl peaks (at 207.91 and 207.85 ppm) were observed, however, presumably due to partial exchange of the carbonyl ^{18}O with $H_2{}^{16}O$. Also, a MS fragment due to the cyclohexyl ring at *m/z* 97 was observed, but no corresponding peak for the ^{18}O labelled compound *m/z* 99 was seen. This indicated that a dioxirane intermediate is not involved in the epoxidation process.

Two other possibilities have not been ruled out, however. The observed *syn*-selectivity could be due to intramolecular epoxidation by either a carbonyl oxide[61] or an α-hydroxyperoxide intermediate.[64, 65] There is precedent in the literature for these intermediates to undergo epoxidation reactions.

Murray generated carbonyl oxides by either photo-oxidation or triphenyl phosphite ozonide oxidation of diazocompounds, and found that the carbonyl oxides formed effected epoxidation of simple alkenes like *cis*-hex-3-ene.[66] As can be seen in Table 15, a variety of conditions was used, resulting in differing isomeric epoxide product ratios. When the carbonyl oxide was produced using triphenyl phosphite ozonide oxidation the epoxide products had a *cis* / *trans* ratio of 84:16. This changed to 55:45 when photo-oxidation was used to generate the carbonyl oxide. Interestingly, when benzophenone

was irradiated in the absence of any diazocompound but in the presence of alkene, epoxidation still occurred to some degree, but now the *cis* / *trans* ratio was 18:82. This change in epoxide ratio was explained by the fact that although theoretical calculations indicated that the carbonyl oxide exists as a planar singlet diradical in its lowest energy state, there are also several other low lying energy states. Murray proposed that the different methods of carbonyl oxide formation generated carbonyl oxides in states other than the lowest energy one. Regardless of the method used for the generation of carbonyl oxides, the alkene geometry is scrambled when epoxidised by one. It is this scrambling of epoxide geometry which can be used to determined the difference between dioxirane and carbonyl oxide epoxidation. In our cyclic systems, however, it is clearly not possible for scrambling of the epoxide geometry to occur so it can not be determined whether or not a carbonyl oxide was responsible for the epoxidation.

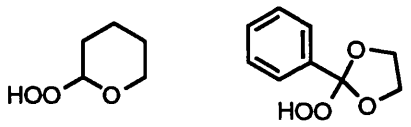


carbonyl oxide generation by:	epoxide (%)	epoxide ratio (*cis* / *trans*)
triphenyl phosphite ozonide	10.4	84:16
photo-oxidation	3.2	55:45
benzophenone (hυ)	0.9	18:82

(Table 15: Carbonyl oxide Epoxidation of *cis*-hex-3-ene)

An α-hydroxyperoxide tetrahedral intermediate (**A**, Scheme 24) as the epoxidising agent is also consistent with the result of the labelling study. Precedent for alkene epoxidation by this type of intermediate can be found in the work of Rebek on α-hydroperoxy ethers[64] and Saito on α-silyloxy peroxyesters.[65] Rebek showed that α-hydroperoxy ethers like those shown in Figure 12 could epoxidise *trans*-β-methyl styrene,[64b] while other α-hydroperoxy ethers generated *in situ* by the action of hydrogen

peroxide on a selection of orthoesters like triethyl orthoacetate and triethyl orthobenzoate epoxidised a variety of simple alkenes in good yield (Table 16).



(Figure 12)

alkene	epoxide (%)
methylcyclohexene	99
β-methyl styrene	85
cycloheptene	68
cyclopentene	95
octene	15

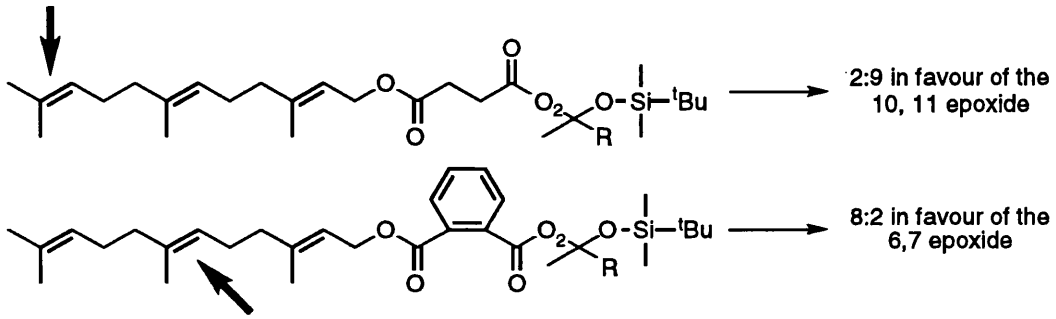
(Table 16: Epoxidation of alkenes by α-hydroperoxy ethers)

Saito used α-silyloxy peroxyesters and a catalytic amount of a copper(II) salt to effect epoxidation of alkenes (Table 17). This system was able to epoxidise cyclic, terminal and non terminal alkenes in good yields.[65a] Saito found that when *cis*-alkenes were epoxidised then a mixture of *cis* / *trans* epoxide isomers resulted, with *cis* isomers predominating.

alkene	reaction time (hr)	yield (%)
trans-stilbene	16	66
trans-oct-2-ene	16	83
cis-oct-2-ene	16	*cis* 72 / *trans* 5
octene	40	43

(Table 17: Epoxidation of alkenes by α-silyloxy peroxyesters)

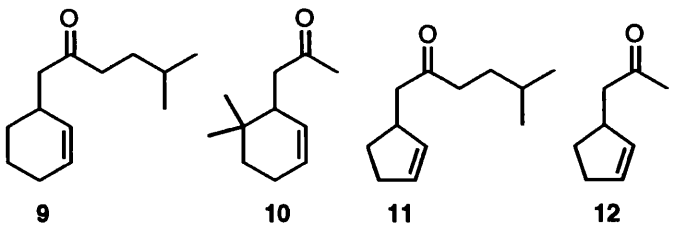
Intramolecular epoxidation of polyalkenes (Scheme 26) by α-silyloxy peroxyesters has also been reported.[65a] Regio-control over the double bond oxidised can be achieved by the use of different ester groups. As can be seen the ethyl linked α-silyloxy peroxyester yields predominantly the product of epoxidation of the 10,11 double bond, while the aryl linked α-silyloxy peroxyester yields predominantly the 6,7 epoxide product. This can be rationalised by the preferred transition state geometries of the different esters during the intramolecular epoxidation process.



(Scheme 26)

Alternatively, the *syn* selectivity seen in the *m*CPBA epoxidation of keto-alkene **1** could be explained by a dipole-dipole interaction between the carbonyl of the keto-alkene and the peracid that is not influenced by the nature of the solvent. Such effects are difficult to predict. It is also difficult to explain why amides are better and esters are poorer than ketones at directing the peracid epoxidation .

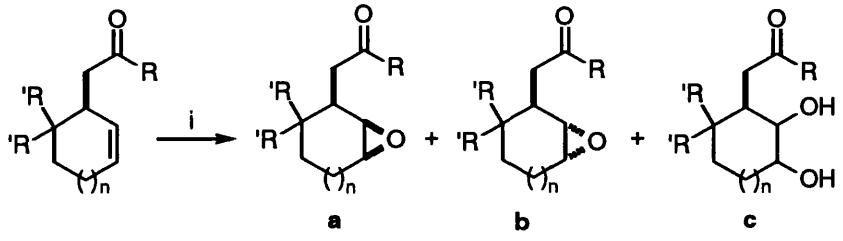
Whatever the reason for the selectivity in the peracid epoxidation of keto-alkene **1**, it was a potentially useful observation and so a range of similar keto-alkenes were studied (Figure 13).[60] Cyclic keto-alkenes were synthesised by reaction of an alkyl lithium reagent with the appropriate acid, under the conditions described earlier.[59] Acids that were not commercially available (*i.e.* the precursor of **10**) were prepared from the appropriate cyclohex-2-en-1-one by Luche reduction[67] to yield the allylic alcohol, followed by Johnson orthoester Claisen rearrangement and hydrolysis of the resulting ester (*cf.* Scheme 22).



9 **10** **11** **12**

(Figure 13)

These keto-alkenes were treated with *m*CPBA (Table 18).



a **b** **c**

Keto-alkenes Products

1 n=1, R = Me, 'R = H
9 n=1, R = $CH_2CH_2CH(CH_3)_2$, 'R = H
10 n=1, R = CH_3, 'R = CH_3
11 n=0, R = $CH_2CH_2CH(CH_3)_2$, 'R = H
12 n=0, R = CH_3, 'R = H

7 n =1, R = Me, 'R = H
13 n=1, R = $CH_2CH_2CH(CH_3)_2$, 'R = H
14 n=1, R = CH_3, 'R = CH_3
15 n=0, R = $CH_2CH_2CH(CH_3)_2$, 'R = H
16 n=0, R = CH_3, 'R = H

Reagents and Conditions: (i), *m*CPBA, solvent (see Table 18).

Entry	Keto-alkene	Product	Solvent[a]	Selectivity[b] **a: b: c**
1	**9**	**13**	ether	4: 0: 1
2	**9**	**13**	CH_2Cl_2	4: 0: 1
3	**10**	**14**	ether	**a** only
4	**11**	**15**	CH_2Cl_2	9: 2: 0
5	**11**	**15**	ether	9: 1: 0
6	**12**	**16**	CH_2Cl_2	5: 1: 0
7	**12**	**16**	ether	10: 1: 0

[a] When CH_2Cl_2 was used as the solvent an equal volume of saturated aqueous $NaHCO_3$ solution was also employed. [b] As measured by ^1H NMR.

(Table 18: *m*CPBA Epoxidation of Cyclic Keto-alkenes)

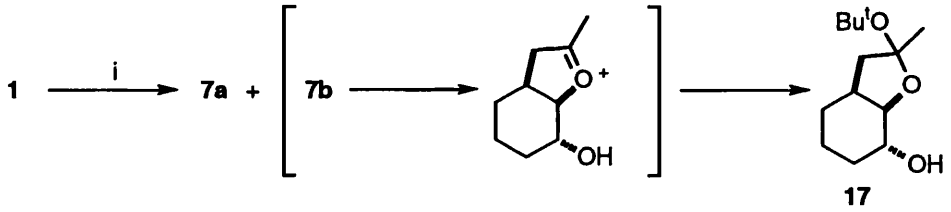
For keto-alkene **10** (Entry 3, Table 18) only the *syn* isomer **14a** was formed. Keto-alkenes **11** and **12** (Entries 4-7, Table 18) yielded a mixture of diastereomeric epoxide isomers. Keto-alkene **9**, however, yielded a mixture of *syn* epoxide **13a** and diol **13c** (Entry 2). The relative configuration of the major keto-epoxides **13a** and **16a** was determined by the series of correlation experiments described earlier for keto-epoxide **7a** (Scheme 23). The relative stereochemistry of **14a, 15a** and **15b** is assumed in view of the similarity between the ^{1}H NMR spectra of **7a, 16a** and **16b** respectively. In the cases of keto-epoxides **14, 15** and **16**, the selectivity was measured by integration of the epoxide protons in the ^{1}H NMR spectrum. As mentioned, in the epoxidation of keto-alkene **9** the *anti* keto-epoxide **13b** was not seen; instead a ^{1}H NMR of the crude product indicated the presence of diol **13c**. This presumably arises from the facile ring opening of the *anti* keto-epoxide **13b**, with neighboring group participation from the carbonyl. Since diol **13c** can also presumably arise from hydrolysis of the *syn* keto-epoxide **13a**, the estimation of the diastereoselectivity based upon measurement of the ratio of *syn* epoxide to diol must be regarded as a lower limit.

In the epoxidation of keto-alkenes **11** and **12**, it can be seen that changing the solvent from CH_2Cl_2 to ether has a dramatic effect. The *syn* selectivity becomes more pronounced in ether than in CH_2Cl_2. This is the opposite of what has been reported in the peracid epoxidation of cyclic allylic alcohols, again suggesting that hydrogen bonding effects are not important in these examples.[68] A possible explanation for the results in Table 18 is that there is a minimisation of dipoles in the transition state. CH_2Cl_2 has a greater dipole moment than ether (1.6 and 1.15 D respectively), and so CH_2Cl_2 can disrupt to a greater extent any dipole alignment between the peracid and the carbonyl group, resulting in lower selectivity in the epoxidation reaction.

Keto-alkene **1** was treated with several other common epoxidation reagents in order to ascertain the generality of the ketone's directing effect. Use of magnesium monoperphthalate[69] (MMPP) in ethanol gave only the *syn* keto-epoxide **7a**. MMPP was also used to epoxidise cyclopent-2-enyl keto-alkene **12** and again the major isomer was the *syn* keto-epoxide, the actual ratio of *syn* / *anti* being determined as 7:1. The origin of

the diastereoselectivity in the MMPP epoxidation of keto-alkenes **1** and **12** is presumably similar to that for the *m*CPBA epoxidation of the same keto-alkenes.

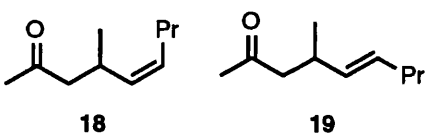
Keto-alkene **1** was also epoxidised using $Mo(CO)_6$ / TBHP. As mentioned previously, Pearson had shown that esters can direct the course of epoxidation reactions under these conditions.[55] A 3:2 mixture of *syn* epoxide **7a** and ketal **17** was observed in the ^1H NMR spectrum of the crude product. Ketal **17** is presumably formed by intramolecular opening of the *anti* keto-epoxide **7b** by the carbonyl group, followed by trapping of the resulting oxonium ion with *tert*-butanol (Scheme 27). A 3:2 ratio of *syn* / *anti* keto-epoxides was detected when keto-alkene **12** was epoxidised in this fashion. It seems that unlike esters, ketones are unable to influence the course of the $Mo(CO)_6$ / TBHP epoxidation reaction to any significant degree. DMDO was also used to epoxidise a range of keto-alkenes, and a full account of these interesting results will be presented later in this thesis.



Reagents and Conditions: (i), $Mo(CO)_6$, TBHP, benzene, reflux.

(Scheme 27)

Having examined the epoxidation of cyclic keto-alkenes, attention was now turned to acyclic systems. These are of greater interest since the resulting keto-epoxides can be transformed into substituted heterocyclic substructures.[2-4] To this end keto-alkenes **18** and **19** (Figure 14) were prepared first. These keto-alkenes were chosen since the double bond, carbonyl group and the chiral centre are in the same relative positions as in cyclic keto-alkene **1**.



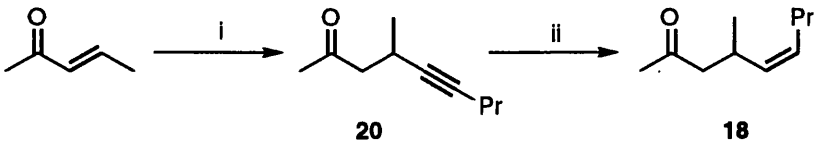
18 **19**

(Figure 14)

Conjugate addition of an acetylide to pent-3-en-2-one was envisaged as yielding a precursor **20** that could be easily transformed into compounds with either alkene geometry. Conjugate addition of copper acetylides is notoriously difficult to achieve; over the last decade several alternative methods have been reported. The first method that was tried involved reacting the lithium acetylide with diethylaluminium chloride.[70] This presumably generated an organoaluminium species which has been reported to undergo 1,4-conjugate addition. Upon quenching and work-up it was discovered that the reaction had yielded a mixture of 1,2-addition, 1,4-addition and 1,2-,1,4-bis-addition products. Although the desired product was isolated it was decided to investigate an alternative procedure for carrying out the conjugate addition.

The second method attempted involved formation of an organozinc reagent. In this reaction, the lithium acetylide was added to a solution of zinc bromide in THF. The enone and TMSOTf were added a short time later,[71] but when the reaction was worked-up it yielded no recognisable products.

The most successful method (Scheme 28) was one that did involve forming an organocopper reagent. The lithium acetylide was added to a suspension of copper(I) iodide, followed by addition of TMSI.[72] This organocopper complex (RCu(LiI)-TMSI) enables the alkyne function to add in a 1,4-manner, the TMSI trapping the enolate formed by the addition. On work-up only one addition product, the desired one, was observed. However, due to the volatility of the product, isolated yields were poor. Hydrogenation of **20** under standard Lindlar conditions furnished keto-alkene **18** in quantitative yields.



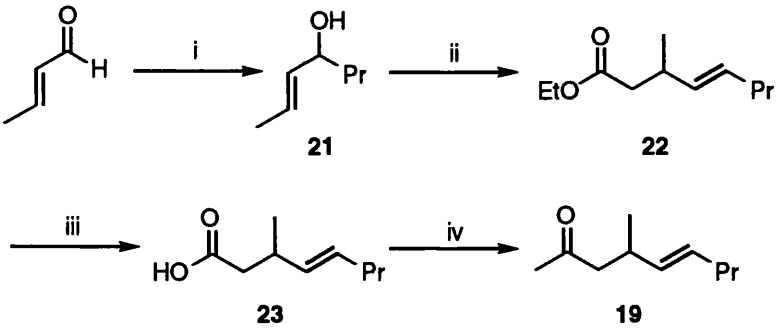
20 **18**

Reagents and Conditions: (i), pentyne, BuLi, CuI, TMSI, Et_2O, -78°C, 10%; (ii), Lindlar catalyst, H_2, hexane, 100%.

(Scheme 28)

Initially, as mentioned above, the *E*-alkene **19** was to be prepared by dissolving metal reduction of keto-alkyne **20**, but this approach was abandoned due to very poor yields.

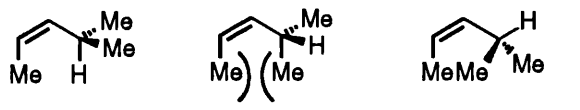
The *E*-alkene was eventually prepared using the sequence of transformations shown in Scheme 29, which are similar to the route used to prepare the keto-alkene **1**. Propyl Grignard addition to crotonaldehyde yielded the secondary allylic alcohol **21**, which was transformed to the ethyl ester **22** by Johnson orthoester protocol. In this acyclic system, none of the allylic acetate was formed. The ester was hydrolysed under standard conditions and the resulting acid **23** was treated with MeLi / TMSCl to yield the desired keto-alkene **19**.



Reagents and Conditions: (i), PrMgCl, Et_2O, 78%; (ii), $CH_3C(OEt)_3$, $C_2H_5CO_2H$, 100%; (iii), NaOH, MeOH, 75%; (iv), MeLi, TMSCl, Et_2O, 40%.

(Scheme 29)

It was reasoned that good diastereoselectivities in the epoxidation reaction could be achieved as the *Z*-keto-alkene **18** was expected to have a marked ground state conformational preference due to avoidance of $A_{1,3}$ strain.[40] Although the concept of allylic 1,3 strain ($A_{1,3}$ strain) was proposed by F. Johnson over 25 years ago,[73] it is only recently that it has received the general attention of synthetic chemists, in particular to explain the high stereoselectivity often observed in additions to *Z*-alkenes with α-chiral centres. The concept of the minimisation of $A_{1,3}$ strain can be explained by considering the case of *Z*-4-methyl pent-2-ene (Figure 15).



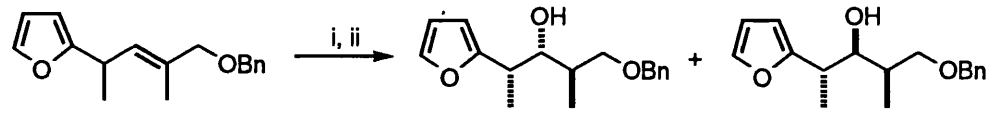
A **B** **C**

0 > +4 kcal mol^{-1} + 3.44 kcal mol^{-1}

(Figure 15)

In this example, the conformational equilibrium strongly favours conformer **A**. In this conformation the hydrogen effectively eclipses the *Z*-substituent and the two groups at the allylic centre are effectively held over either face of the double bond. Conformer **B** is destabilised by > 4 kcalmol^{-1} over **A** by $A_{1,3}$ strain to the point that **B** now represents an energy maximum determining the rotational barrier. Conformer **C**, although being an energy minimum, lies 3.44 kcalmol^{-1} above conformer **A** and can therefore be neglected when considering the conformer equilibrium. Thus for an allylic system of the type shown in Figure 15 having a *Z* substituent at the double bond, conformer **A** is strongly favoured since in this conformation $A_{1,3}$ strain is avoided. The marked conformational preference exhibited in these systems has been used to great effect in the control of acyclic stereocentres in natural product synthesis. *E*-alkenes lack this conformational preference and additions to them are usually less selective.

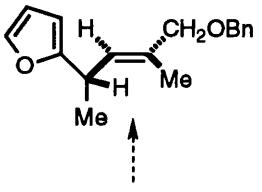
Kishi used the conformational bias in allylic systems to great effect in his synthesis of monensin.[74] Kishi showed that hydroboration of **24** yielded **25** and its diastereomer in a 8:1 ratio in favour of **25** (Scheme 30).[74a] This selectivity was rationalised by $A_{1,3}$ strain dictating a conformational preference for **24** (Figure 16), leading to hydroboration occurring on the less hindered face of the double bond, *syn* to the methyl group. The other possible conformations of **24** would be disfavoured due to the reasons stated above.



24 **25** **8 : 1**

Reagents and Conditions: (i), B_2H_6, THF, 0°C; (ii), NaOH, H_2O_2, 85%.

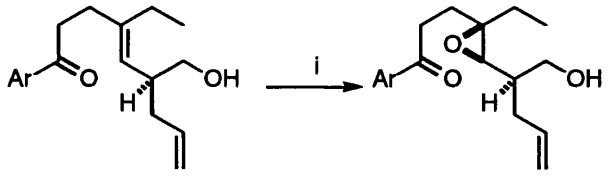
(Scheme 30)



attack on the same face of the double bond as the Me group

(Figure 16)

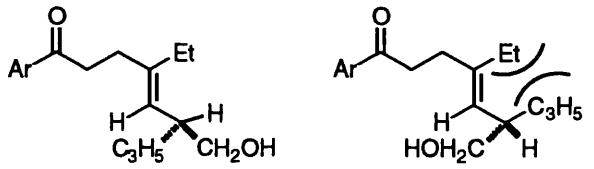
Later in the same synthesis of monensin,[74b] Kishi exploited the minimisation of $A_{1,3}$ strain again in the hydroxyl directed *m*CPBA epoxidation of **26** to yield epoxide **27** exclusively (Scheme 31). The stereoselectivity of the epoxidation was rationalised by **26** adopting conformation **A** (Figure 17) over conformation **B** (Figure 17), due to the avoidance of $A_{1,3}$ strain. Hydroxyl directed epoxidation would then lead to epoxidation of the double bond *syn* to the hydroxyl group.



26 **27**

Reagents and Conditions: (i), *m*CPBA, CH_2Cl_2, (aq) $NaHCO_3$.

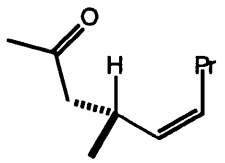
(Scheme 31)



A **B**

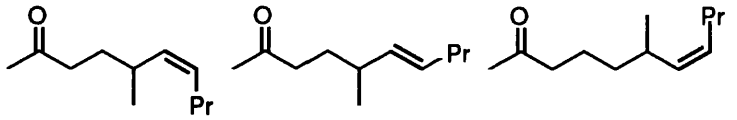
(Figure 17)

Based on these ideas of $A_{1,3}$ strain, the preferred conformation of keto-alkene **18** is where the proton at the chiral centre eclipses the propyl group on the alkene (Figure 18). This conformational preference (as illustrated below) should ensure differentiation of the diastereotopic faces of the alkene, with the ketone side chain effectively held over one of them.



(Figure 18)

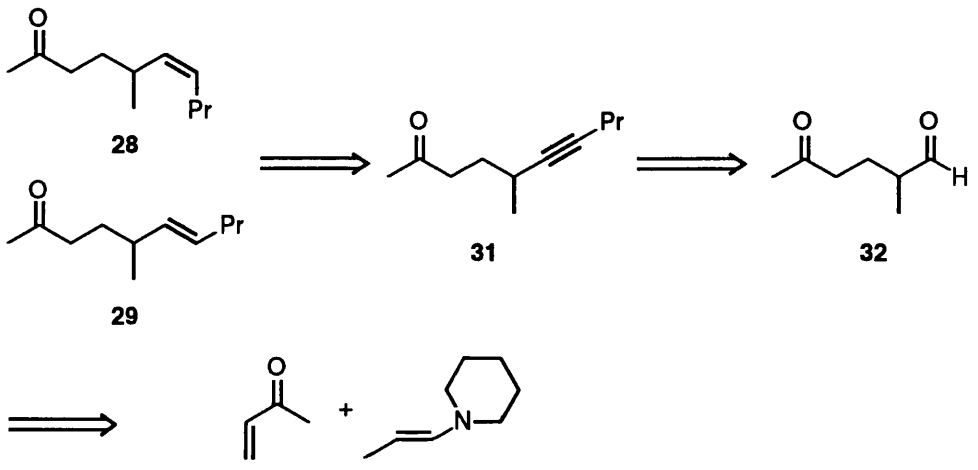
However, epoxidation of **18** with *m*CPBA resulted in what was essentially a 1:1 mixture of diastereomeric epoxides. Less surprisingly, the *E*-isomer **19**, lacking the $A_{1,3}$ strain conformational lock, also generated a 1:1 mixture of epoxides on treatment with *m*CPBA. The main reasons for the lack of selectivity in the epoxidation of **18** were considered to be that the tether between ketone and alkene was too short to allow an intramolecular process to occur without considerable deviation from the preferred ($A_{1,3}$ strain) conformation. This would reduce the energy difference between the diastereomeric transition states, and also slow the intramolecular process with respect to the intermolecular background epoxidation by *m*CPBA. Keto-alkenes **28**, **29** and **30** (Figure 19) possess extended tethers so the distortion detailed above should not occur.



28 **29** **30**

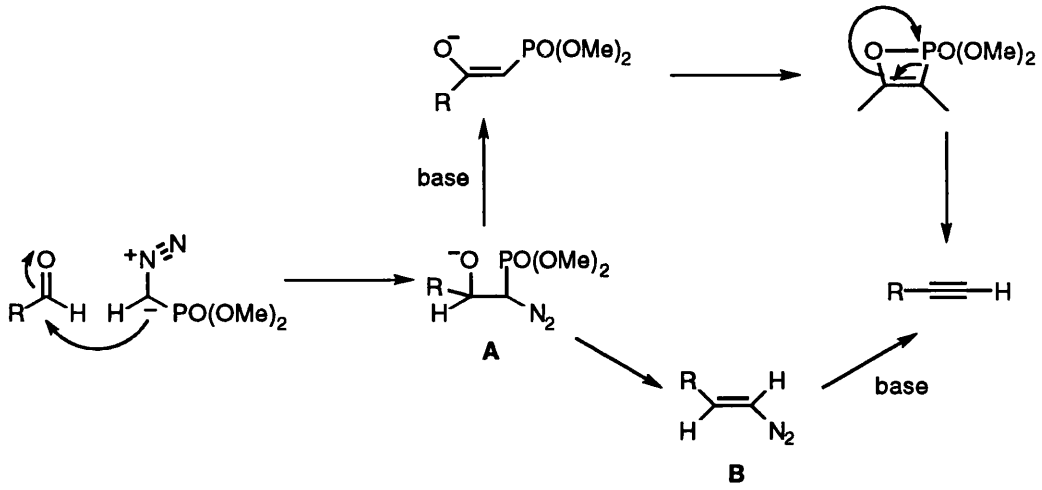
(Figure 19)

Keto-alkenes **28** and **29** were envisaged as coming from a common precursor, keto-alkyne **31**, by use of the appropriate reduction methods (Scheme 32). The *Z*-isomer **28** was to come from Lindlar hydrogenation of keto-alkyne **31**, and the *E*-isomer from a dissolving metal reduction of **31**. The required keto-alkyne **31** was to be prepared by addition of the appropriate Gilbert reagent (described below) under modified Colvin-Hamil conditions to known keto-aldehyde **32**.



(Scheme 32)

The Gilbert modification[75] of the Colvin-Hamil reaction[76] involves the use of diazophosphonates to effect the transformation of an aldehyde or an aromatic ketone to an alkyne in one step. Aldehydes yield terminal alkynes (Scheme 33) and aromatic ketones are transformed to diaryl alkynes.

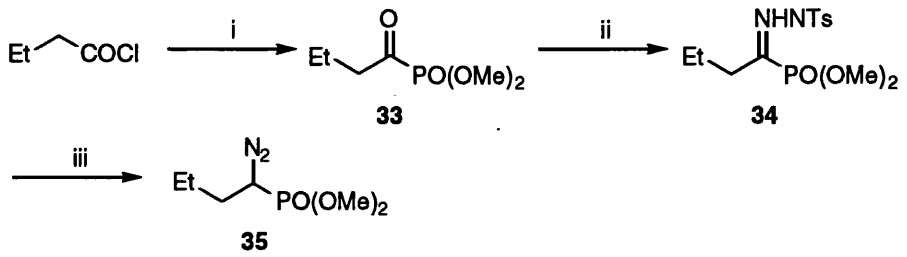


(Scheme 33)

The reaction is carried out in THF under nitrogen using ^{t}BuOK as base. In their original paper[76] Colvin and Hamil used BuLi to effect irreversible deprotonation of the intermediate (either **A** or **B**, Scheme 33). Gilbert showed that better yields were obtained when ^{t}BuOK was used instead.[75] The reaction was assumed to proceed *via* addition of the diazophosphonate to the carbonyl group, followed by elimination of nitrogen and then of the phosphorus oxide, or *vice versa*. A search of the literature revealed that this methodology has thus far only been used for the synthesis of terminal aliphatic or diaryl alkynes. The extension of this methodology to disubstituted aliphatic alkynes is an obvious progression.

The required diazophosphonate was prepared by literature methods[77] summarised in Scheme 34. Trimethyl phosphite was dripped slowly into an ethereal solution of butyryl chloride, the solvent and residual starting materials being distilled away after overnight stirring to yield keto phosphonate **33** quantitatively. *p*-Toluenesulfonyl hydrazone **34** was obtained by stirring **33** in methanol with *p*-toluenesulfonyl hydrazine, the crystals of **34** being filtered away after 24 hours. Diazophosphonate **35** was obtained by stirring

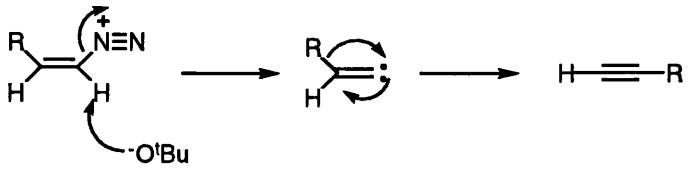
hydrazone **34** in a ether / water biphase with potassium carbonate, the resulting diazophosphonate **35** being partitioned into the organic phase. The other reaction partner, keto-aldehyde **32**, was prepared by the condensation of the piperidine enamine of propanal with methyl vinylketone, followed by hydrolysis with aqueous oxalic acid solution.[78]



Reagents and Conditions: (i), trimethyl phosphite, Et_2O, 100%; (ii), tosyl hydrazine, MeOH, 76%; (iii), K_2CO_3, H_2O, Et_2O, 46%.

(Scheme 34)

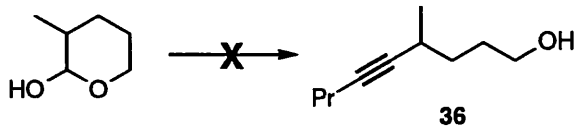
Attempted alkyne formation from **32** and **35** under reported conditions[75] failed to furnish any of the desired keto-alkyne **31**. Starting material was recovered in all cases. This led to the conclusion that the increased steric congestion of the propyl group over that of a proton in our substituted diazophosphonate caused the addition reaction to be unfavourable. Recently, however, it has been suggested that the reaction proceeds *via* formation of a vinylidenecarbene intermediate[79] (Scheme 35). If this is the case then it will prove impossible to extend the methodology to the formation of non terminal alkynes, as the diazophosphonates required would not be able to form the carbene needed for the rearrangement to the alkyne.



(Scheme 35)

As an alternative route, addition of diazophosphonate **35** to α-methyl valerolactol, prepared by DIBAL reduction of α-methyl valerolactone, was also attempted (Scheme

36). This approach failed to generate any alkyne **36**, which it was thought could have been converted into **31** by the standard but laborious sequence of oxidation, methyl Grignard addition and oxidation.

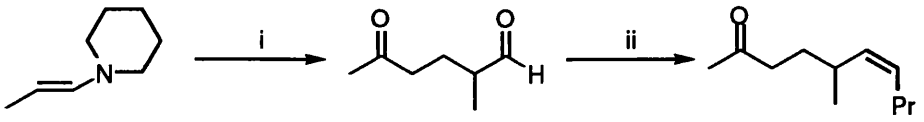


36

Reagents and Conditions: (i), **31**, ^{t}BuOK, THF.

(Scheme 36)

After successive failures with the Colvin-Hamil route it was decided to construct the *E* and *Z* alkenes by alternative olefination strategies. The *Z*-alkene would now be obtained by Wittig methodology (Scheme 37), and the *E*-alkene was envisaged to arise from Julia olefination of keto-aldehyde **32**. The route detailed in Scheme 37 involved selective formation of an alkene at the aldehyde terminus of **32**, while not effecting the transformation on the ketone end. It was reasoned that this would succeed given the higher reactivity of aldehydes. There was slight doubt; as the aldehyde has a methyl group α to it, this could affect the addition of the ylide and make addition to the ketone competitive.



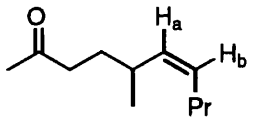
32 **28**

Reagents and Conditions: (i), methyl vinylketone, oxalic acid, 100%; (ii), NaHMDS, $Ph_3P^+C_4H_9Br^-$, toluene, 85%.

(Scheme 37)

Upon conducting the Wittig reaction in toluene with BuLi as base, it was observed that olefination occurred at only the aldehyde terminus, but yielded a 1:1 mixture of inseparable geometric double bond isomers. When the base was changed to NaHMDS in toluene only one geometric double bond isomer was formed. This was confirmed as

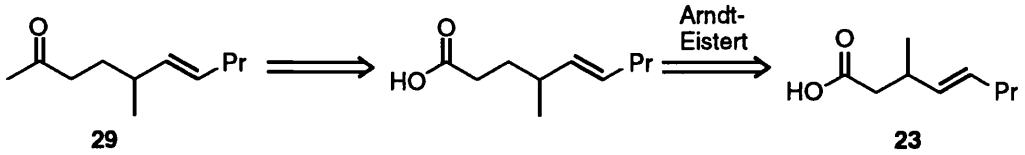
having the *Z* configuration by nOe difference experiments (Figure 20). The adjacent alkenic protons had nOe values of 4.9% and 6.6% to each other.



H_a-H_b = 4.9%
H_b-H_a = 6.6%

(Figure 20: nOe difference experiments on keto-alkene **28**)

The sulfone required for the Julia olefination was prepared by the reaction of sodium phenolthiolate with butyl bromide, and oxidation of the resulting sulfide with Oxone®. The olefination was conducted under standard Julia conditions, but after addition of Na / Hg amalgam only starting materials were isolated. We are unable to explain why only starting materials were recovered. In a final attempt to prepare keto-alkene **29**, a strategy was adopted that would incorporate the problematic double bond at an earlier stage. This was to be achieved *via* an Arndt-Eistert homologation of acid **23** (Scheme 38), which was prepared *en route* to keto-alkene **19**. TMS-diazomethane was used to generate the diazo-ketone precursor of the carbene needed to effect homologation. Work-up, however, returned only starting acid **23**. It was at this point that parallel investigations into the mechanism of the intramolecular dioxirane epoxidation reaction (described later in this thesis) led us to abandon the synthesis of the *E*-alkene isomers.

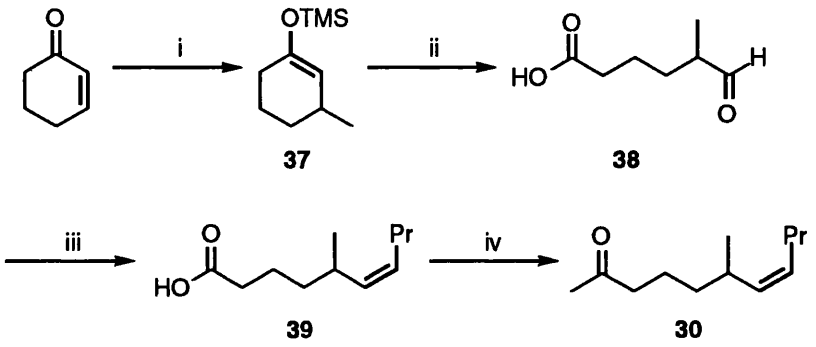


29 **23**

(Scheme 38)

Keto-alkene **30** was prepared according to the route shown in Scheme 39. Conjugate addition of methylcopper to cyclohex-2-en-1-one was performed using conditions reported by Johnson and Marren.[80] This involved generation of methylcopper *in situ* by addition of MeLi to copper(I) iodide. The conjugate addition is facilitated by the presence

of TMSCl which enhances the rate of the reaction, and TMEDA which stabilises and solubilises the organocopper. The TMEDA also increases the reactivity of the silyl halide. The product silyl enol ether **37** was immediately ozonised[81] to yield **38**. Wittig olefination and MeLi addition followed the same general procedure that was mentioned earlier. A nOe difference experiment again confirmed the double bond geometry as *Z*, each alkenic proton having an nOe of 10% to the other.



Reagents and Conditions: (i), MeLi, CuI, TMEDA, TMSCl, Et_2O; (ii), O_3, Me_2S, MeOH, CH_2Cl_2, 41% over two steps; (iii), $Ph_3P^+C_4H_9Br^-$, NaHMDS, toluene, 80%; (iv), MeLi, TMSCl, THF, 61%.

(Scheme 39)

*m*CPBA epoxidation of **28** and **30** led in each case to a 1:1 mixture of diastereomeric epoxides. Since models suggest that intramolecular epoxidation can occur without deviation from the preferred ($A_{1,3}$ strain) conformation, it seems that direct and non-selective epoxidation by *m*CPBA is responsible for the lack of selectivity. A more flexible tether would indeed be expected to slow any intramolecular process relative to direct intermolecular epoxidation by *m*CPBA.

2.2: Conclusions

It has been shown that the ketone carbonyl group can direct the course of peracid epoxidation of a series of cyclic alkenes. This directing effect is greater than that expected on the basis of the carbonyl's ability to form hydrogen bonds to the peracid. Indeed, the selectivity has in all cases been shown to be greater than in the peracid epoxidation of the corresponding ester. An ^{18}O labelling experiment has been used to show that this selectivity does not arise from dioxirane formation. It is possible that the selectivity arises from the intramolecular epoxidation of the alkene by a tetrahedral hydroxyperoxide intermediate. Given the decreased selectivity observed in the epoxidation of certain keto-alkenes in solvents of a high dipole moment it is also possible that subtle dipole-dipole interactions are involved in the selectivity seen. Unfortunately, acyclic keto-alkenes fail to undergo stereoselective epoxidation , and as a result of this there are no plans at present to further pursue this area of directed epoxidation. Although this methodology could not be extended to the acyclic keto-alkenes, it does provide incentive to find a system with no direct background epoxidation. The biphasic, ketone accelerated epoxidation of alkenes with Oxone® is one such possible system[5] and our investigations into this will be discussed in Chapter 4.

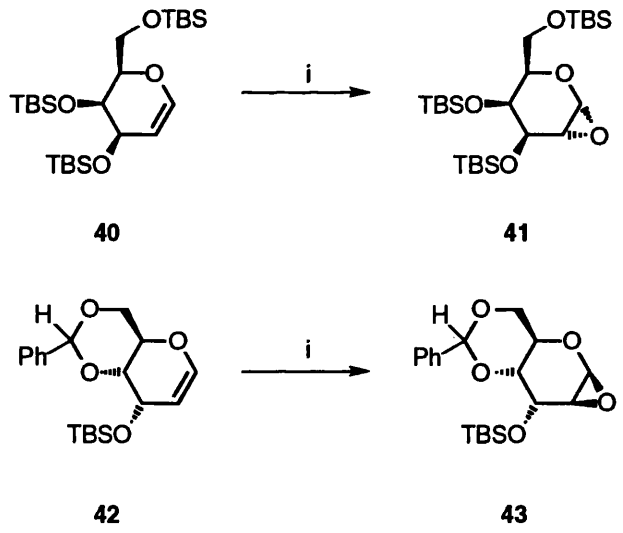
Chapter 3:

DMDO Epoxidation of Cyclic, Carbonyl-Containing Alkenes

3.1: Results and Discussion

3.1i: DMDO Epoxidation of the Cyclic Keto-alkenes

The investigation into carbonyl directed peracid epoxidation of cyclic keto-alkenes generated some interesting results, but an authentic sample of *anti* keto-epoxide **7b** had yet to be prepared. As mentioned briefly earlier, DMDO was used in the epoxidation of keto-alkene **1**.[60b] Upon evaporation of the acetone a ^{1}H NMR of the crude reaction mixture showed that the reaction had yielded a 1:1 mixture of *syn* keto-epoxide **7a** and diol **7c**. The formation of the diol **7c** was surprising, as DMDO has been used with great effect to prepare acid sensitive epoxides. Danishefsky[82] used isolated DMDO / acetone solution to epoxidise galactal derived **40** and allal-derived **42**, to yield epoxides **41** and **43** respectively (Scheme 40). It is worthy to note that under standard peracid conditions, epoxides of this type undergo hydrolysis to generate the appropriate diols.

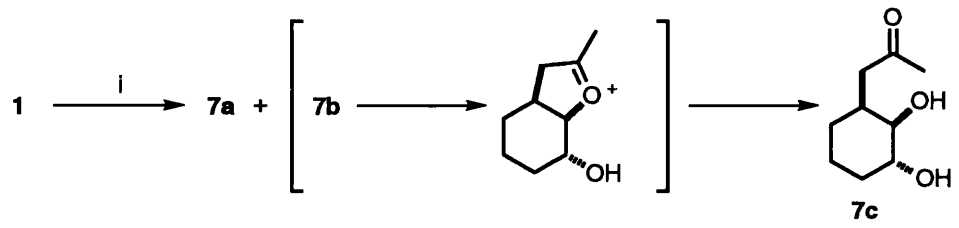


Reagents and Conditions: (i), DMDO, acetone.

(Scheme 40)

It was believed that diol **7c** arises from the facile ring opening of *anti* epoxide **7b** with neighboring group participation from the ketone carbonyl (Scheme 41), and its stereochemistry was tentatively assigned on this assumption. The mechanism for the formation of diol **7c** was investigated using ^{18}O labelled keto-alkene **1a**. After treatment

of **1a** with DMDO, MS analysis revealed substantial transfer of the ^{18}O label to one of the hydroxyl groups, since a peak in the E.I. spectrum due to loss of CH_3COCH_2- side chain was observed at *m/z* 116. The corresponding peak due to unlabelled diol at *m/z* 114 was not significant. This seems to indicate that the mechanism for the formation of diol **7c** is indeed as suggested in Scheme 41.

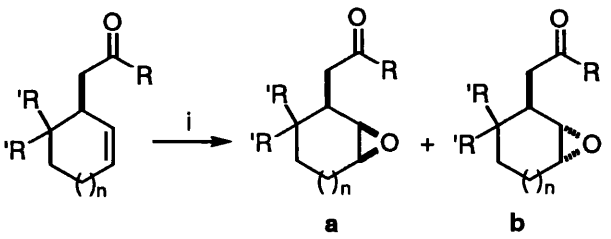


Reagents and Conditions: (i), DMDO, acetone.

(Scheme 41)

The DMDO solution used in this reaction had been dried with anhydrous K_2CO_3 and stored over powdered molecular sieves at -20°C. It was later discovered that when the DMDO solution was dried with only K_2CO_3, the expected diastereomeric epoxides **7a** and **7b** were obtained in a *syn / anti* ratio of 2.5:1. It is therefore probable that the presence of a small amount of Lewis acidic molecular sieves in the reaction mixture was responsible for promoting diol formation. The difference in the observed ratio of products using DMDO dried in different ways may actually reflect a change in the diastereoselectivity of the epoxidation, but it is more likely that diol **7c** can also arise from hydrolysis of *syn* keto-epoxide **7a**. This means that the *syn / anti* selectivity measured based on the diol represents a lower limit only.

An authentic sample of *anti* keto-epoxide **7b** had now been prepared, but more interesting was the *syn* selectivity of the DMDO epoxidation. Keto-alkenes **9**, **10**, **11** and **12** were treated with DMDO and *syn* keto-epoxides were found to predominate in all cases (Table 19).



a **b**

Keto-alkenes

1 n=1, R = Me, 'R = H
9 n=1, R = $CH_2CH_2CH(CH_3)_2$, 'R = H
10 n=1, R = CH_3, 'R = CH_3
11 n=0, R = $CH_2CH_2CH(CH_3)_2$, 'R = H
12 n=0, R = CH_3, 'R = H

Products

7 n=1, R = Me, 'R = H
13 n=1, R = $CH_2CH_2CH(CH_3)_2$, 'R = H
14 n=1, R = CH_3, 'R = CH_3
15 n=0, R = $CH_2CH_2CH(CH_3)_2$, 'R = H
16 n=0, R = CH_3, 'R = H

Reagents and Conditions: (i), DMDO / acetone.

Keto-alkenes	Products	Ratio[a] *syn* (**a**) / *anti* (**b**)
1	**7**	2.5 : 1
9	**13**	2.5 : 1
10	**14**	2 : 1
11	**15**	4 : 1
12	**16**	4.5 : 1

All reactions were performed by adding DMDO / acetone solution (1.25 equiv. of 0.1M) to neat keto-alkenes. a) Ratio determined by ^1H NMR.

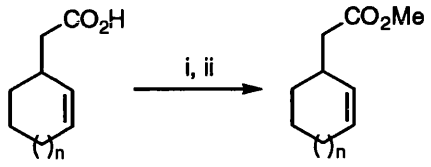
(Table 19: Selectivities in the DMDO Epoxidation)

Although it is impossible for DMDO to form a tetrahedral intermediate with the keto-alkenes as proposed for the directed peracid epoxidation, we reasoned that it might be possible for DMDO to insert an O atom into the C=O bond of the carbonyl group forming another dioxirane. If this was the case, the newly formed dioxirane could undergo intramolecular epoxidation to generate the *syn* keto-epoxides. To test this theory, keto-epoxide **7a**, derived from DMDO epoxidation of ^{18}O labelled keto-alkene **1a**, was analysed by MS and ^{13}C NMR. Examination of these spectra showed that no ^{18}O label transfer to the epoxide had occurred, effectively eliminating the possibility of a trans-dioxiranation process.

At the time that this work was performed, little was known about directing effects in the DMDO epoxidation reaction, so it was decided to study this aspect of the chemistry of

this useful reagent. Esters, amides and carbamates have been shown to direct the course of peracid epoxidation of cyclic alkenes,[50, 51] so an investigation of their influence on the DMDO epoxidation reaction was undertaken.

3.1ii: DMDO Epoxidation of Cyclic Esters, Amides and Carbamates

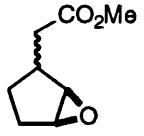
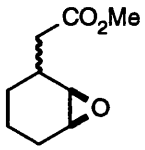


3, n=1 **44**, n=0
45, n=1

Reagents and Conditions: (i), oxalyl chloride, CH_2Cl_2; (ii), MeOH.

(Scheme 42)

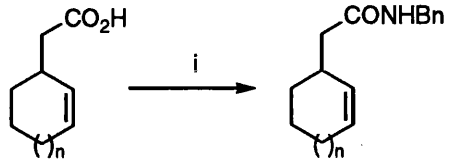
Treatment of commercially available 2-cyclopenten-1-acetic acid or **3** with oxalyl chloride in CH_2Cl_2 generated the corresponding acid chlorides which were treated with methanol to yield esters **44** and **45**. These esters were separately treated with DMDO / acetone solution. On evaporation of the solvent it was found that the *syn* epoxy-ester predominated (Table 20). Proof that the *syn* epoxy-ester was indeed the major product came from comparison of the ^1H NMR spectra of the products to the ^1H NMR spectra of authentic samples, prepared by the iodolactonisation route described earlier (Scheme 23).

substrate	product	ratio[a] *syn* (**a**) / *anti* (**b**)
44	 **46**	5.5 : 1
45	 **47**	3 : 1

All reactions were performed by adding DMDO / acetone solution (1.25 eq. of 0.08M) to neat ester. [a] Ratio determined by ^1H NMR.

(Table 20: Selectivities in the Ester Directed DMDO Epoxidation)

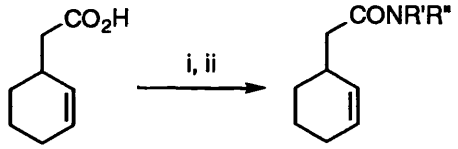
Amides **48** and **49** were prepared by DCC coupling of the appropriate acids with benzylamine as reported by Kocovsky (Scheme 43).[50b] Amides **50** and **51** were prepared by treating the acid chloride with the desired amine using the Schotten-Baumann procedure (Scheme 44).



3, n=1 **48**, n=0
49, n=1

Reagents and Conditions: (i), benzyl amine, HOBT, DMF, DCC.

(Scheme 43)

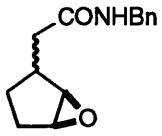
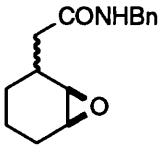
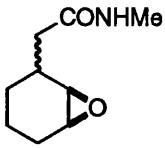
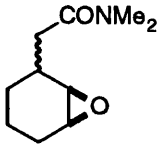


3 **50**, R'=H, R"=Me
51, R'=R"=Me

Reagents and Conditions: (i), oxalyl chloride, CH_2Cl_2; (ii), NaOH(aq), methyl amine (**41**) (or dimethyamine (**42**)), CH_2Cl_2.

(Scheme 44)

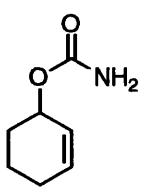
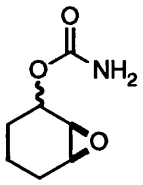
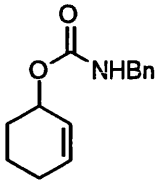
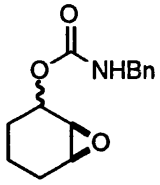
As for esters and ketones, when amides **48-51** were treated with DMDO / acetone solution, *syn* epoxy-amides were the major products (Table 21). The major epoxides formed in this reaction were found to be spectroscopically identical to the major epoxide products produced by treatment of amides **48-51** with *m*CPBA.[50] This indicated that the major epoxides formed by the reaction with DMDO were *syn*.

substrate	product	ratio[a] *syn* (**a**) / *anti* (**b**)
48	 **52**	5 : 1
49	 **53**	3 : 1
50	 **54**	11 : 1
51	 **55**	3.7 : 1

All reactions were performed by adding DMDO / acetone solution (1.25 eq. of 0.08M) to neat amide. [a)] Ratio determined by ^{1}H NMR.

(Table 21: Selectivities in the Amide Directed DMDO Epoxidation)

Carbamates have been shown to direct peracid epoxidation of cyclic alkenes with a greater degree of selectivity than either esters or amides.[50] For this reason, known carbamates **56** and **57** (Table 22) were prepared and treated with DMDO / acetone solution. Analysis of the ^{1}H NMR spectra of the crude reaction products revealed that the *anti* epoxy-carbamate isomers predominated (Table 22). Like the epoxy-amides above, the relative stereochemistry was determined by the preparation of authentic samples of the *syn* epoxy-carbamate products by *m*CPBA epoxidation,[50] and comparison of the ^{1}H NMR spectra.

substrate	product	ratio[a] *syn* (**a**) / *anti* (**b**)
 **56**	 **58**	1 : 2
 **57**	 **59**	1 : 2

All reactions were performed by adding DMDO / acetone solution (1.25 eq. of 0.08M) to neat carbamate.
a) Ratio determined by ^{1}H NMR.

(Table 22: Selectivities in the DMDO Epoxidation of Cyclic Carbamates)

The directing effect exhibited by certain carbonyl containing compounds on the course of the DMDO epoxidation reaction is not easy to explain. In the case of ketones it was feasible for a trans-dioxiranation process to be involved, although ^{18}O labelling experiments proved this not to be the case. It would not, however, be possible to explain the selectivity exhibited by esters and amides in this manner. While some of the amides have an acidic proton capable of hydrogen bond formation, **50** is the only amide to show higher selectivity than the esters. It is also impossible to invoke a hydrogen bonding mechanism for the selectivities seen in the epoxidation of cyclic esters. One explanation which has been invoked previously[54, 56] to explain the selectivity in DMDO epoxidation of cyclic functionalised alkenes is the alignment of dipoles between the directing functionality and DMDO. It is reasonable to suggest that a transition state conformation exists where the dipole of DMDO aligns itself *anti* parallel to the dipole of the carbonyl group, lowering the energy of the transition state for *syn* epoxidation. Ketones, esters and amides all have dipoles of various sizes pointing in the same general direction. It is reasonable to assume that carbamates, however, have either a smaller dipole or a dipole oriented in the opposite direction to ketones, esters and amides. It may be that this factor

is responsible for the observation that for these substrates, there is either no directing effect or a slight preference for the *anti* epoxide isomer.

Amide **50** exhibits an anomalously large *syn* / *anti* ratio of epoxides when compared to the other amides. This could well be due to hydrogen bond formation between the amide NH and an oxygen of DMDO, enhancing the *syn* selectivity. These results are comparable to the results of Murray[56] which are discussed in the introduction. The results presented here along with those of Murray support the idea that substrates which are able to form hydrogen bonds to DMDO generate epoxides in greater diastereoselectivity than those that can not. Although Murray did not study homoallylic amides he did study esters similar to ones included in our study. He too found that the epoxidation favoured the formation of the *syn* epoxide, with a ratio of *syn* / *anti* epoxides very similar to the ratios observed by us.

Acyclic keto-alkenes **18, 19, 28** and **30** were independently treated with DMDO / acetone solution and the resulting epoxide mixtures analysed. It was found that in all cases, both epoxide diastereoisomers were formed in equal amounts. The lack of selectivity may be explained by the fact that in the acyclic systems the dipole of the carbonyl group is too far removed to influence the epoxidation and so background epoxidation predominates.

3.2: Conclusion

It has been shown that the carbonyl groups of ketones, esters and amides direct the course of DMDO epoxidation of cyclic alkenes. Carbamates have been shown not to direct the DMDO epoxidation reaction. It is believed that although in one case hydrogen bond formation between an acidic proton and DMDO may account for some of the observed selectivity, this is not the major contributing factor. A dipole-dipole interaction between the carbonyl and DMDO has been used to explain the selectivities seen. The anomalous results exhibited by carbamates are thought to be explained by the fact that the dipole of a carbamate is fundamentally different than those of ketones, esters and amides. Unfortunately, like the peracid epoxidation, this method can not be used to direct the

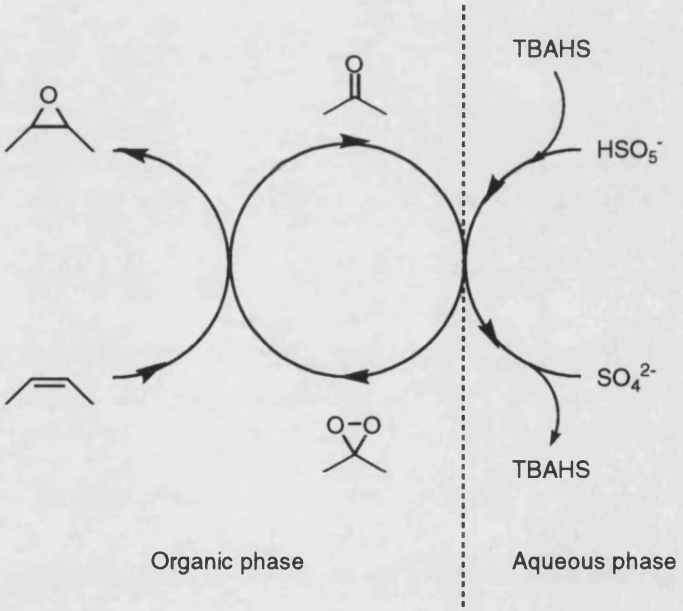
course of epoxidation in acyclic keto-alkenes. The largest directing effects were observed for amides, so further work in this area may be conducted to examine whether *acyclic* secondary amides can direct the course of the DMDO epoxidation reaction.

Chapter 4:

The Biphasic Ketone-Oxone® System

4.1: Results and Discussion

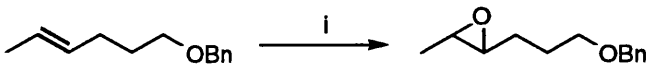
The lack of selectivity in the epoxidation of acyclic keto-alkenes with *m*CPBA or DMDO provided great incentive to study a system where background epoxidation in the absence of ketone does not occur. The two phase Oxone® system mentioned earlier[5] was viewed as a good way of accomplishing this. The mechanism of the reaction (Scheme 45) was thought to be that Bu_4NHSO_4 carried the Oxone® into the organic phase. Once the HSO_5^- was in the same phase as the ketone it could attack the ketone carbonyl and form a dioxirane. It was thought that this dioxirane epoxidised the alkene regenerating the original ketone. In the absence of a ketone no epoxidation took place.[5] In the presence of a ketone and the absence of an alkene, dioxiranes have been isolated by distillation from these solutions.[21, 83]



(Scheme 45)

As mentioned earlier, Denmark has completed a comprehensive and systematic study of the biphasic system, which has enabled the optimum conditions for the catalytic epoxidation to be determined.[20] As will be seen, there are many inter-related variables that must be examined and understood; this will be illustrated by a discussion of the study conducted by Denmark and co-workers. First to be investigated by Denmark was the

stoichiometry of the reagents. In previous studies by Curci,[5, 13] a large excess of both Oxone® and ketone was employed. A set of arbitrary conditions were set by Denmark: (i) all reactions were to be run at 0°C and at a pH of 7.8, (ii) the rate of addition of Oxone® to the reaction would be 1 equiv. / min of 0.4M solution and (iii) the alkene to be used was *E*-6-benzyloxy-2-hexene (Scheme 46).



Reagents and Conditions: (i), CH_2Cl_2, buffer, Oxone®, catalyst (see Table 25), 0°C

(Scheme 46)

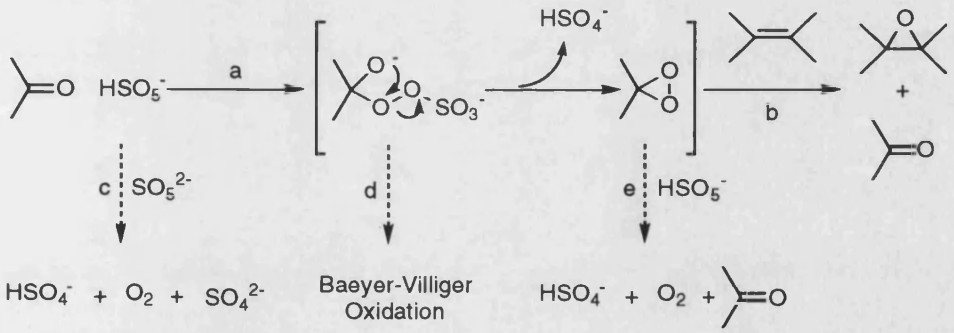
Denmark discovered that the efficiency of the epoxidation reaction could be optimised by the careful control of the reaction conditions such as pH of the reaction, stoichiometry of the Oxone® and the ketone, rate of addition of the Oxone® and the structure of the ketone used. Each of these will be discussed in turn. It was found that control of the pH of the reaction was critical for a good conversion to epoxide to be achieved (Table 23). Conversion of the alkene to the epoxide is reduced if the pH is below 7.5. This is attributed to two reasons. The first is that there is little anion present to attack the ketone. The second is irreversible consumption of ketone by Baeyer-Villiger oxidation (path **d**, Scheme 47). This pathway can be minimised by strict pH control (> 7) and by the use of ketones that are slow to undergo Baeyer-Villiger oxidation, *i.e.* ketones that contain groups of low migratory aptitude. At high pH, caroate exists as the more nucleophilic dianion and reaction of this with HSO_5^- to form sulfate and oxygen occurs (path **c**, Scheme 47), leading to the destruction of caroate[84] and reduced conversion to the epoxide. Thus as can be seen from Table 23, the optimum pH for the epoxidation reaction is in the narrow range of 7.8 - 8.0.

Time (hrs.)	Conv. (%) pH 7.0	Conv. (%) pH 7.5	Conv. (%) pH 7.8	Conv. (%) pH 8.0	Conv. (%) pH 8.5
10	20	50	58	70	10
15	26	60	80	90	10

All reactions were performed using ketone **61** (10 mol%) (see below) at 0°C with 0.1 equiv. of Bu_4NHSO_4. The rate of addition of Oxone® (10 equiv.) to the reaction was 1 equiv. / min of 0.4M solution. Conversion was measured by GC analysis.

(Table 23: Effect of pH on the Ketone - Oxone® Epoxidation Reaction)

Surprisingly, increasing the amount of Oxone® in the reaction does not increase the amount of epoxide formed. This is due to another Oxone® consuming pathway (path **e**, Scheme 47). In an Oxone® rich environment, dioxiranes can promote the destruction of Oxone®. Indeed, this was shown by Edwards and Curci in their ^{18}O labelling study described earlier.[12] Denmark found that Oxone® consumption by this pathway could be reduced by the slow addition of Oxone® (*ca.* 480 mins) to the system, thus keeping the Oxone® concentration low. Interestingly, increasing the amount of Bu_4NHSO_4 in the reaction did not increase the rate of the conversion of alkene to epoxide. Denmark was unable to explain this result.



(Scheme 47)

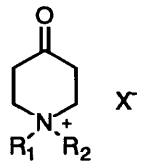
The final factor that did have a dramatic effect on the rate of the epoxidation was the amount and type of ketone used. Denmark found that with 0.1 equiv. of Bu_4NHSO_4, 10 equiv. of Oxone® and 1 equiv. of acetone, the reaction was 50% complete after 24 hrs. A similar reaction but with 10 equiv. of acetone was found to be 100% complete after the

same period of time. Denmark then investigated the effect of ketone structure on the epoxidation reaction using the optimum conditions described earlier. It was found that acyclic ketones possessing substitution α- to the carbonyl group were less effective at promoting the reaction than acetone. Of the cyclic ketones studied only cyclohexanone promoted the epoxidation with the efficiency of acetone (Table 24). As simple aliphatic ketones were for the most part unable to promote the epoxidation reaction with any degree of efficiency, Denmark decided to examine ketones like *N,N*-dimethyl-1,4-oxopiperidinium nitrate. As mentioned earlier this ketone has been shown to be 1300 times more effective than acetone at the oxidation of chloride,[11] but when tested in Denmark's epoxidation system it failed to promote any epoxidation. Denmark reasoned that *N,N*-dimethyl-1,4-oxopiperidinium nitrate was capable of forming a dioxirane, but was unable to transfer oxygen to the alkene. Further *N,N*-dialkyl-1,4-oxopiperidinium salts were synthesised with differing nitrogen substitution and were used as catalysts in the biphasic epoxidation reaction (Table 25).

Entry	Ketone	Conversion (%)
1	acetone	87
2	2-butanone	40
3	3-pentanone	5
4	cyclobutanone	2
5	cyclopentanone	3
6	cyclohexanone	67
7	1,1,1,-trifluoroacetone	29
8	hexafluoroacetone	2

All reactions performed in CH_2Cl_2 / H_2O (pH 7.8) with 2 equiv. of ketone and 10 mol% of Bu_4NHSO_4 at 0°C for 24 hrs.

(Table 24: Effect of Ketone Structure on the Epoxidation of *E*-6-benzyloxy hex-2-ene)



Entry	Ketone	R_1	R_2	^-X	Conv. (%)
1	**60**	Me	Me	NO_3	< 5
2	**61**	Me	$C_{12}H_{25}$	OTf	> 92
3	**62**	C_6H_{13}	C_6H_{13}	OTf	22
4	**63**	Me	$C_{18}H_{37}$	OTf	< 5
5	**64**	Me	$C_{12}H_{25}$	NO_3	59

All reactions were performed using ketone (10 mol%) at 0°C and pH 7.8. The rate of addition of Oxone® (10 equiv.) in a 0.4M solution to the reaction was 480 mins. Conversion was measured by GC analysis.

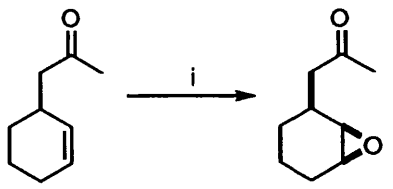
(Table 25: Denmark's Ketones)

As can be seen, both highly lipophilic (**63**) and hydrophilic (**60**) salts are virtually inactive as promoters. This inactivity arises from the fact that both **60** and **63** are unable to shuttle between the phases of the reaction. Hydrophilic **60** spends most of its time in the aqueous phase, so although it decomposes Oxone® efficiently[11] it rarely comes into contact with the alkene. On the other hand, lipophilic **63** spends most of its time in the organic phase and so never comes into contact with the Oxone®. It would seem that chain length and not just carbon count (**61** vs. **62**) is important, although Denmark was uncertain as to why this should be the case.

With an understanding of the complexities of the ketone - Oxone® biphasic epoxidation system, it is now possible to continue with a discussion of the intramolecular reaction. At the outset of our work, the Denmark study was yet to be published, but the crucial need for pH control had already been established.[5, 84] Investigation into the intramolecular biphasic epoxidation reaction began by use of the original conditions reported by Curci.[5] Curci's original conditions were to add a solution of Oxone® (12 mmol) in water (30 cm^3) over *ca.* 30 mins to a biphase of CH_2Cl_2 (50 cm^3) and pH 7.2 phosphate buffer (20 cm^3) at 5°C containing keto-alkene (5.1 mmol) and Bu_4NHSO_4 (1

mmol). During the addition the pH was monitored and controlled by pH stat. addition of 0.5M KOH solution. The reaction was found to be complete after 3 hrs.

In our initial studies using keto-alkene **1** (Scheme 48), it was exceedingly difficult to control the pH to the level required with any accuracy. This was a result of the dosing equipment overdosing the reaction, leading to swings in the pH during the course of the reaction. To reduce the amount of base added, the molarity of KOH was decreased from 0.5M to 0.1M. This merely had the effect of increasing the aqueous volume present, and did not resolve the dosing problem. In a deviation from Curci's work, it was decided to premix the Oxone® solution (0.48M before pre-neutralisation) with 0.5M KOH until pH 7.5 was reached. It was felt that this would facilitate pH control. The technique of adding a pre-neutralised solution of Oxone® to the reaction had not previously been reported. This is presumably due to the instability of Oxone® at pHs near to neutral (path **c**, Scheme 47). This was indeed a problem, for although the reaction proceeded with no swings of pH (small additions of 0.5M KOH were added dropwise *via* pipette when needed), after 3 hrs. the reaction was found to be only 10% complete. In the next attempt to simplify the reaction conditions, additional quantities of Oxone® were added over the course of the reaction. To minimise the aqueous volume, these additions were of solid Oxone®. Unfortunately, it became impossible to control the pH to the degree of accuracy required and the reaction mixture became too acidic. Upon neutralisation and work-up, no recognisable products were observed. In an attempt to compensate for the decomposition of Oxone® at near neutral pH and hence increase the conversion to epoxide, the next experiment involved using a large excess of Oxone® and one equivalent of Bu_4NHSO_4 with respect to keto-alkene **1**. Still using the pre-mixing technique to control the pH, it was under these conditions that the first promising results appeared (Table 26). Although we had found an easy way to control the pH of the epoxidation reaction, we had to pay the price of using a large excess of Oxone® to push the reaction to completion.



1 **7a**

Reagents and Conditions: (i), Oxone®, $EDTANa_2$, 0.5M KOH, CH_2Cl_2, Phosphate buffer pH 7.2, TBAHS.

(Scheme 48)

Entry	$KHSO_5$ (mmol)[a]	TBAHS (mmol)	CH_2Cl_2 (cm^3)	Time (hrs)	Conv. (%)[b]	Ratio[b] *syn / anti*	Yield (%)
1	23.8	0.3	5	24	100	*syn*	60
2	11.9	0.3	5	24	66	5 : 1	*syn* 35 *anti* 16
3	17.9	0.3	5	24	100	*syn*	46
4	14.9	0.3	5	24	100	*syn*	50
5	14.9	none	none	< 6	100	3.6 : 1	*syn* 54 *anti* 6
6	14.9	none	5	24	85	3.5 : 1	*syn* 46
7	14.9	0.3	2.5	24	100	*syn*	55
8	14.9[c]	none	none	4.5	100	3.8:1	*syn* 46 *anti* 16

Keto-alkene **1** (50 mg, 0.36 mmol) and phosphate buffer pH 7.2 (5 cm^3) (Aldrich) was used in all the epoxidation reactions reported in Table 26. [a] Oxone® 0.48M solution with $EDTANa_2$ (12.5 mg) was pre-mixed with 0.5M KOH until the pH was 7.5. This solution was added over 45 mins. [b] As measured by ^1H NMR syn: 3.14 and 3.08 ppm, anti: 3.15 and 2.84 ppm. [c] Oxone® was added as a 0.24M solution with $EDATNa_2$ (12.5 mg).

(Table 26: Optimisation of the Biphasic Conditions)

As can be seen (entry 1, Table 26) these conditions generated exclusively the *syn* keto-epoxide **7a** in moderate yield. (It is believed that the slightly disappointing yields are due to the volatility and water solubility of the product.) The amount of Oxone®, and hence the volume of the aqueous phase, was systematically reduced (entries 2-4, Table 26). This was in an attempt to minimise both of the above quantities and to make the

reaction more efficient in Oxone®. This was achieved (entry 4, Table 26), but when less Oxone® than 14.9 mmol was used (entry 2, Table 26) not only did the conversion drop but there was also a change in the ratio of diastereomeric epoxides formed. The reduced conversion may be explained by the fact that the reduced amount of Oxone® decomposes before the reaction is complete. The change in ratio however is not as easy to explain.

As mentioned previously, Ford showed that an aqueous solution of Oxone® is capable of the rapid epoxidation of alkenes in the absence of ketone.[15] We subjected keto-alkene **1** to these conditions in an attempt to determine the inherent diastereoselectivity for the epoxidation, in what we considered would be predominantly direct attack by Oxone® on the double bond. Indeed, when this reaction was run, a 3.6 : 1 ratio of diastereomeric epoxides was formed (entry 5, Table 26). Evidence for the direct epoxidation of keto-alkene **1** by Oxone® in the aqueous system, was obtained when the concentration of the aqueous layer was halved (entry 8, Table 26). Under these conditions epoxidation generated a mixture of diastereomeric epoxides in a *syn* / *anti* ratio of 3.8 : 1. This, when compared to entry 5, Table 26, showed that dilution of the reaction resulted in little change in the epoxide ratio. If the reaction was intramolecular then dilution would be expected to increase the *syn* / *anti* ratio of epoxides. When CH_2Cl_2 was added (entry 6, Table 26) the mixture became a biphase. Under these conditions the conversion dropped, presumably due to keto-alkene **1** and the Oxone® now being in separate phases. The ratio of epoxides remained unchanged at 3.5 : 1, suggesting that the species responsible for alkene epoxidation in entry 5, Table 26 is also responsible for the epoxidation seen in entry 6. When this result was compared to entry 4, Table 26 where Bu_4NHSO_4 has been added, it seemed that our goal had been achieved. The conversion in entry 4, Table 26 was 100%, indicating that the oxidant and keto-alkene **1** were now in the same phase. More important, however, was the fact that the ratio of epoxides had changed. Now only the *syn* keto-epoxide **7a** had formed. This suggested that there had been a change in oxidising species. This was attributed to Bu_4NHSO_4 carrying Oxone® into the organic phase where it could attack the ketone carbonyl. This in turn would lead to dioxirane formation, the dioxirane then being able to epoxidise the double bond in an intramolecular fashion.

The effect of concentrating the organic layer was examined next (entry 7, Table 26). It was reasoned that increasing the concentration of the organic layer would result in intermolecular dioxirane epoxidation becoming more favoured over the competing intramolecular dioxirane pathway, which should lead to a reduction in the *syn / anti* ratio of the epoxide products. It was found, however, that the concentration of the organic phase could be increased without adverse effect on the ratio of the epoxide products. The lack of ratio change associated with the reduction in the volume of CH_2Cl_2 can be attributed to one of three possibilities: (i) at this concentration the intramolecular reaction still predominated over the intermolecular reaction, (ii) the reaction is intermolecular at all concentrations or (iii) the reaction occurs in the aqueous phase. Which of these is the case will be discussed later in this thesis.

For this methodology to be of use to the synthetic organic chemist, an easy-to-use and efficient means of buffering the reaction needed to be developed. Such a system had already been reported in a closely related context by Ford[15] and Corey[14] who showed that in the epoxidation of simple alkenes by an aqueous solution of Oxone®, the reaction could be buffered by adding 1.4 equiv. of 1M $NaHCO_3$ solution (with respect to Oxone®) at the start of the reaction. This buffering system works as the $KHSO_4$ generated in the reaction is neutralised by the $NaHCO_3$. This yields H_2CO_3, which decomposes to give water and CO_2, which evaporates from the reaction. This loss of acid from the system as CO_2 results in a slow rise in the pH of the reaction, starting at about 7 and slowly rising to about 8 during the reaction.[15] This procedure alleviated the need for constant pH control and dropwise addition of base. For the rest of the studies detailed in this thesis into the nature of the biphasic system, this modification to the reaction conditions was used. In our hands this method of $NaHCO_3$ buffering gave identical results for the epoxidation of **1** to the pre-neutralisation procedure (described earlier) for buffering the reaction (Table 27). The Oxone® solution could now be added to the reaction mixture without dropwise addition or pre-neutralisation with base. The reaction would now buffer itself, with no further addition of base required. In these experiments the pH would typically start around 7.2 and increase over the course of the reaction's 24

hr duration to about 8.4. This modification also reduced the aqueous volume of the reaction to a more manageable quantity.

Entry	$KHSO_5$ (mmol)	TBAHS (mmol)	CH_2Cl_2 (cm^3)	Buffer (cm^3)	Time (hrs)	Conv. (%)[c]	Ratio[c] *syn / anti*
1[a]	14.9	0.3	2.5	phosphate 5	24	100	*syn*
2[b]	14.9	0.3	2.5	$NaHCO_3$ 22	24	100	*syn*

Keto-alkene **1** (50 mg, 0.36 mmol) was used in all the epoxidation reactions reported in Table 27. [a] Oxone® 0.48M solution with $EDTANa_2$ (12.5 mg) was pre-mixed with 0.5M KOH until the pH was 7.5. This solution was added over 45 mins. [b] Oxone® 0.48M solution with $EDTANa_2$ (12.5 mg) was added without pre-mixing in one portion to the reaction mixture. [c] As measured by ^1H NMR.

(Table 27: The use of $NaHCO_3$ as a Buffer in the Biphasic System)

4.1i: Mechanistic Studies on the Biphasic System using ^{18}O labelled Ketones

Conditions had been developed that generated exclusively *syn* keto-epoxide **7a**, so a program of experiments was undertaken to prove that this was indeed a dioxirane mediated process. To determine whether or not the epoxidation of **1** to yield **7a** was a dioxirane mediated process, ^{18}O labelled keto-alkene **1a** was epoxidised using the biphasic conditions. It was reasoned that providing attack by caroate on the carbonyl was stereorandom, a dioxirane would be produced with a distribution of ^{16}O and ^{18}O in each diastereotopic oxygen. With intramolecular dioxirane epoxidation, a partitioning of the ^{18}O label between the carbonyl group and the epoxide should occur. As in the case of the mechanistic study on the *m*CPBA epoxidation,[60] the extent of the label transfer was to be determined by MS and ^{13}C NMR.

Keto-alkene **1a** was subjected to the reaction conditions as shown in entry 2, Table 27. There was some concern that the aqueous reaction conditions may result in the loss of the ^{18}O label from the ketone. Keto-epoxide **7a** was purified by column chromatography on silica neutralised with a 1% solution of triethylamine in the mobile phase. This was to

stop any acid catalysed ^{18}O / ^{16}O exchange in the ketone and to stop any epoxide ring opening. Analysis of **7a** by ^{13}C NMR showed only one carbonyl peak, at *ca.* 208 ppm, and one set of epoxide resonances, at 55.1 and 53.5 ppm. When this sample was mixed with a non-labelled sample of keto-epoxide **7a** the ^{13}C NMR showed a doubling of the carbonyl peaks, at 208.399 and 208.344 ppm, but no doubling of the epoxide peaks. This indicated that no ^{18}O label transfer to the epoxide had occurred. This was verified by MS analysis where the ring fragment *m/z* 97 corresponded to only the unlabelled epoxide, no labelled ring fragment *m/z* 99 being observed. This result suggested that a dioxirane was not responsible for the epoxidation.

Unfortunately, there is no way to measure the rate of epoxidation of keto-alkene **1** in the absence of a carbonyl group, so there is no way to know whether the carbonyl group in keto-alkene **1** actually accelerates the reaction (*ie.* is actually involved at all in the epoxidation process). For this reason it was decided to investigate the intermediacy of dioxiranes in the related intermolecular biphasic reaction, where the rate of epoxidation can be measured in the absence of a ketone.

Investigation into the intermediacy of dioxiranes in the established biphasic intermolecular reaction began by examination of our $NaHCO_3$ buffered reaction conditions in the absence and presence of acetone. Firstly, the epoxidation of cyclohexene was examined (Table 28). Conversion of the alkene to epoxide for these and the ^{18}O labelled experiments on the intermolecular system was measured by GC / MS. Aliquots were withdrawn from the reaction at 5 hrs. and analysed using a Fisons MD-800 GC / MS; DD-1 25 m x 0.25 mm column, film thickness 0.25 μm. The relative intensities of the cyclohexene and cyclohexene oxide peaks were noted for a known equimolar mixture in CH_2Cl_2. This enabled accurate determination of the conversion of the reaction without the need to add an internal standard.

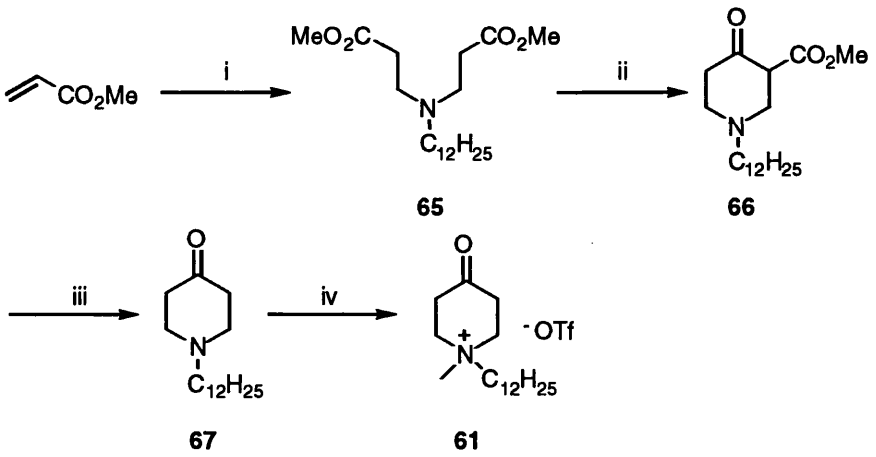
Entry	$KHSO_5$ (mmol)[a]	TBAHS (mmol)	CH_2Cl_2 (cm^3)	acetone (mmol)	Conv.[b] (% at 5 hrs)
1	12	0.2	50	none	2.5
2	12	0.2	50	5	16

Cyclohexene (5 mmol) and 1M $NaHCO_3$ (17 cm^3) was used in all the reactions reported in Table 28, which were run at 0°C. [a] Oxone® was added as a 0.4M solution with $EDTANa_2$ (20 mg) in one portion. [b] As measured by GC analysis.

(Table 28: The Acetone Promoted Epoxidation of Cyclohexene by Oxone®)

In agreement with the work of Curci, very little epoxidation occurred in the absence of acetone.[5] When the reaction containing 1 equivalent of acetone with respect to cyclohexene was run, the conversion increased from 2.5% to 16%. This conversion may appear low, but it is worth mentioning that in his original paper, to achieve quantitative conversion to the epoxide in 5 hrs, Curci had to use 10 equiv. of acetone. Due to the practical difficulties associated with ^{18}O labelling and isolating the ^{18}O labelled sample of acetone, it was decided to use another promoter for the reaction.

As mentioned earlier, the most efficient promoter of the reaction to date is the class of ketone reported by Denmark (Scheme 49). These molecules combine the properties of a quaternary ammonium salt and a ketone, eliminating the need for an added phase transfer catalyst. The most efficient of these ketone promoters was synthesised according to Denmark's procedure.[20] This synthesis is summarised below in Scheme 49. Methyl acrylate was added to a solution of dodecyl amine in methanol. When the reaction was judged complete by TLC (33% EtOAc - petrol) the solvent was distilled away. Dieckman cyclisation yielded the β-keto ester **66**, which was decarboxylated by heating to reflux in 2M HCl to yield **67**. The quaternary ammonium salt was formed by treatment of **67** with methyl triflate in CH_2Cl_2. Recrystalisation from 66% EtOAc - petrol yielded ketone **61**. Ketone **61** was used as a promoter in the biphasic reaction and was, as reported, vastly superior to acetone (Table 29). As in the other studies of the intermolecular reaction, cyclohexene (5 mmol) and a 0.4M solution of Oxone® were used.



Reagents and Conditions: (i), dodecyl amine, methanol, 0°C, 95%; (ii), NaH, PhMe, reflux, 58%; (iii), HCl, reflux, 68%; (iv), MeOTf, CH_2Cl_2, 63%.

(Scheme 49)

Entry	$KHSO_5$ (mmol)[a]	TBAHS (mmol)	CH_2Cl_2 (cm^3)	ketone (mmol)	Conv.[b] (% at 5 hrs)
1	12	0.2	50	acetone (5)	16
2	12	none	50	**61** (5)	57

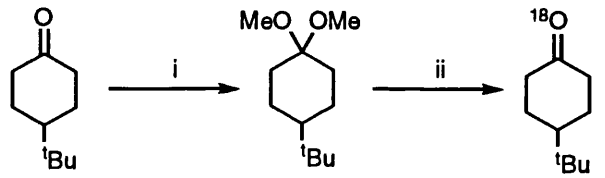
Cyclohexene (5 mmol) and 1M $NaHCO_3$ (17 cm^3) was used in all the reactions reported in Table 29, which were run at 0°C. [a] Oxone® was added as a 0.4M solution with $EDTANa_2$ (20 mg) in one portion. [b] As measured by GC analysis.

(Table 29: Denmark's ketone as a promoter in the Oxone® Epoxidation of Cyclohexene)

Several attempts were made to install an ^{18}O label into ketone **61** *via* its dimethyl ketal. The first method tried was heating ketone **61** to reflux in a 1:1 mixture of methanol / 2,2-dimethoxypropane with catalytic *p*-toluenesulfonic acid and molecular sieves. Unfortunately, it was impossible to follow this reaction by either TLC or IR. Neither the starting material **61** or the product ketal ran on TLC, presumably due to the quaternary ammonium salt present. The IR was for the most part obscured by methanol, and even when there appeared to be no carbonyl group present, the reaction proved to be difficult to work-up. An aqueous work-up generated a thick emulsion that could not be dispersed, and would have presumably resulted in loss of a sizable amount of product. Removal of

solvent concentrated the *p*-toluenesulfonic acid present and catalysed the deprotection reaction; a sample of ketal was never isolated. Similar problems arose when an attempt was made to form the ketal of **67**. This is believed to be due to *p*-toluenesulfonic acid forming a salt with the tertiary amine in the molecule. Even when an excess of *p*-toluenesulfonic acid was used, no ketal could be isolated. Due to the inherent difficulties in producing ^{18}O labelled **61**, it was decided to attempt ^{18}O labelling of another ketone that can accelerate the biphasic epoxidation reaction.

The ketone that was finally used for the ^{18}O label investigation was 4-*tert*-butylcyclohexanone.[85] This ketone would have none of the handling difficulties associated with either acetone or cyclohexanone, and it should be relatively easy to ^{18}O label using the methodology employed for keto-alkene **1a**. 4-*tert*-butylcyclohexanone was ^{18}O labelled according to the series of reactions shown in Scheme 50.



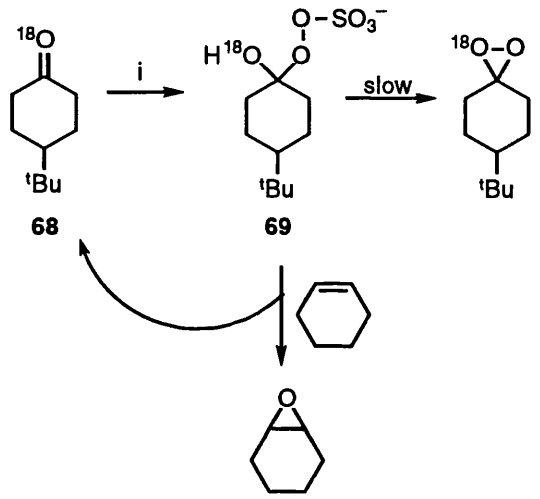
68

Reagents and Conditions: (i), MeOH, 2,2-dimethoxy propane, cat. TsOH, reflux, 94%; (ii), $H_2{}^{18}O$, cat. H_2SO_4, THF, 50%.

(Scheme 50)

Analysis of ketone **68** by MS and ^{13}C NMR revealed that the label incorporation was 50%. Two peaks of equal intensity were present in both the MS (^{16}O ketone M^+=154 and ^{18}O ketone M^+=156) and the ^{13}C NMR (212.60 and 212.56 ppm). A sample of the ^{18}O labelled ketone was used in the biphasic epoxidation system and the reaction was followed by GC / MS. After 5 hrs the conversion was found to be 15%, indicating that the ketone catalyses the reaction under these conditions equally as well as acetone. MS analysis of the epoxide product formed in the reaction showed that the epoxide contained ^{16}O exclusively. There was no incorporation of the ^{18}O label into the product. Analysis of the recovered ketone showed that there was no loss of ^{18}O label from the carbonyl. Assuming that the ketones studied catalyse the reaction in the same manner, it can be

concluded from the lack of ^{18}O label transfer that a dioxirane is not the species responsible for epoxidation in this biphasic system. If a dioxirane is not the intermediate responsible for the epoxidation in this system then what are the other possibilities? One possibility is that caroate adds to the carbonyl group, but transfer of oxygen from the resultant tetrahedral intermediate (**69**, Scheme 51) to the alkene occurs faster than ring closure to the dioxirane. It is known that in the absence of an alkene dioxiranes can be isolated from these mixtures.[21, 83] The explanation given above would account for this fact, as well as the results obtained from the ^{18}O labelling experiment.



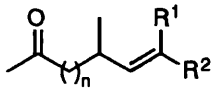
Reagents and Condtions: (i), Oxone®,TBAHS, $(EDTA)Na_2$, 1M aqueous $NaHCO_3$, CH_2Cl_2, 0 °C.

(Scheme 51)

There is the possibility, albeit unlikely, that the acceleration seen in the epoxidation reaction is due to dioxirane formation. The lack of label transfer would then have to be rationalised by another explanation. One possible explanation for the lack of label transfer is a primary kinetic isotope effect. Although possible, this seems unlikely as any primary kinetic isotope effect is liable to be small; k_{16O} / k_{18O} has been calculated as 1.073 for cleavage of a hypothetical C-O molecule at 25°C, but the observed values have been considerably lower.[86] Due to the stereochemical bias of 4-*tert*-butylcyclohexanone it is possible that there may be a further explanation for the lack of ^{18}O label transfer, that is, that the addition of caroate to the carbonyl occurs with high selectivity. This would

generate a dioxirane with the ^{18}O label in exclusively either the axial or the equatorial position. Lack of label transfer would than require that one of the two oxygens be transferred selectively to the alkene. If attack occurred exclusively from the axial trajectory, then this would generate a dioxirane with an ^{18}O label exclusively in the equatorial position. This would mean that if a dioxirane was involved in the epoxidation, oxygen transfer to the alkene would have to take place exclusively from the more hindered axial position, a situation that seems somewhat unlikely.

Whatever the reactive intermediate is in the ketone accelerated biphasic Oxone® epoxidation, conditions had been devised that generated exclusively one diastereoisomer in the case of keto-alkene **1**. Acyclic keto-alkenes **18**, **19**, **28** and **30** were submitted to the reaction conditions used to epoxidise keto-alkene **1** (Table 30).



18: n=1, R^1=Pr, R^2=H
19: n=1, R^1=H, R^2=Pr
28: n=2, R^1=Pr, R^2=H
30: n=3, R^1=Pr, R^2=H

Entry	Keto-alkene[a]	Conversion (%)[b]	Ratio of epoxides[c]
1	**18**	100	3 : 2
2	**19**	100	1 : 1
3	**28**	22	not determined
4	**30**	8	not determined

a) Oxone® (14.9 mmol as a 0.48M solution) with $EDTANa_2$ (12.5 mg) was added in one portion to the keto-alkene (0.36 mmol) as a 0.072M solution in CH_2Cl_2 with Bu_4NHSO_4 (0.3 mmol). 1M $NaHCO_3$ (22 cm^3) was used to buffer the reaction. b) At 24 hrs as measured by ^1H NMR. c) As measured by ^{13}C NMR.

(Table 30: Oxone® Epoxidation of Acyclic Keto-alkenes)

Keto-alkenes **18** and **19** were converted completely to their epoxides within 24 hrs; however, the ratio of epoxides was disappointing. It was hoped, as explained earlier, that $A_{1,3}$ strain would provide sufficient conformational bias to influence the course of the epoxidation reaction. The reason for the lack of selectivity was believed to be due to the

reasons outlined in Chapter 2, section 2.1: the molecule having to distort out of its preferred ground state conformation (due to $A_{1,3}$ strain) to effect intramolecular epoxidation. Great hopes were held for keto-alkenes **28** and **30**. These ketones, with their extended tethers, should give epoxide products with greater diastereoselectivity, as distortion from the preferred conformation during the intramolecular epoxidation should not occur. Unfortunately, due to the conversion of keto-alkenes **28** and **30** being very much reduced, 22% and 8% respectively, the diastereoselectivity was not determined.

One explanation for the lower conversion of these substrates with extended tethers is that the intramolecular reaction is slowed with respect to the self decomposition of caroate. Another explanation is as the tether length increases, so the molecules become more lipophilic and so less water soluble. At this point it is relevant to discuss the lipophilicity of organic molecules and how it is measured.

4.1ii: Investigations into the Effect of Increased Lipophilicity of the Keto-alkenes in the Biphasic Oxone® Epoxidation Reaction

The logP value of a compound describes the manner in which it is partitioned between the polar and non-polar phases of a biphasic mixture.[87] LogP values have over the years been used to predict the transport properties and activities of a variety of drugs, pesticides and other xenobiotics.[88] The logP value of a compound is conventionally measured in an octanol / water mixture and is generally termed the $\log P_{oct}$ value of a molecule. Measurement of this parameter, although simple, can often be time consuming. The general procedure for the determination of logP values is described below.

A known weight of solute is dissolved in the most appropriate phase of the solvent pair (most likely octanol for an organic molecule) and then the second phase, usually water is added. The mixture is mechanically shaken for about 30 minutes and then centrifuged for 1-2 hrs. A sample of one of the layers (most usually the water layer) is submitted for GC analysis and the result is compared to a standard solution of known weight of the same solute / solvent pair. The partition value (P) of a compound is then given by the equation:

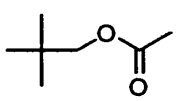
$$P = \frac{\text{integral of standard} - \text{integral of partitioned}}{\text{integral of partitioned}} \times \frac{\text{vol. of water}}{\text{vol. of octanol}}$$

It is often the case, especially in the pharmaceutical industry, that knowledge of the logP value of a molecule is required to determine whether the molecule has the necessary properties in a biological system. It would be a great waste of time and effort to synthesise a potential drug candidate only to measure its logP value and find that it was too lipophilic. Because of this, several methods for the calculation of logP values (clogP is the term given to calculated logP values) of organic solutes have been developed. The method used for the determination of clogP values in this thesis was the hydrophobic fragmental constant approach devised by Rekker.[89, 90] In this approach, Rekker suggested that the total logP of a molecule was the sum of the individual logP values of its constituent parts. This can be expressed as:

$$\log P = \sum_{i}^{n} a_n f_n$$

where a is the number of times a given fragment is present in the molecule and f is the hydrophobic fragmental constant, the lipophilicity contribution of a constituent part of the molecule to its total lipophilicity. For example, 2,2-dimethyl propyl acetate (Figure 21) can be broken into the following parts: 4 (CH_3), CH_2, C and COO. This implies that in Rekker's system the logP value is given by:

$$\log P = 4f(CH_3) + f(CH_2) + f(C) + f(COO)$$



(Figure 21)

The values of the hydrophobic fragmental constants for each component were determined by solving the appropriate equations for a set of 87 different structures. This

calculation provided clogP values for 11 types of structural units: CH_3, CH_2, CH, NH_2, NH, N, C_6H_5, OH, O, COOH and COO. Later, even more structural types were analysed and clogP values were calculated for other structural units such as halogens, carbonyl, NO_2, CF_3, SO and others. A list of these clogP values is presented below (Table 31).

Fragment	hydrophobic fragmental constant	standard deviation
CH_3	0.702	0.021
CH_2	0.527	0.006
CH	0.236	0.022
NH_2	-1.380	0.041
NH	-1.864	0.037
C_6H_5	1.896	0.027
OH	-1.440	0.036
COOH	-1.003	0.035
COO	-1.281	0.041
C=O	-1.69	----
NO_2	-1.02	----
CF_3	0.79	----
SO	-2.75	----
CN	-1.13	----
C (quaternary)	0.15	----

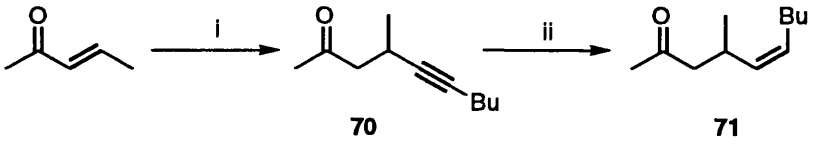
(Table 31: Rekker's hydrophobic fragmental constants for selected structural units)

The hydrophobic fragmental constants calculated by Rekker were used to determine the clogP values of all our keto-alkenes. These values are displayed in Table 32. It was decided to test the validity of the lipophilicity theory by testing keto-alkenes of greater lipophilicity in the biphasic system and monitoring their conversion. Keto-alkene **71** (Scheme 52) was identical to **18** in all aspects except that instead of a propyl group a

butyl group was used instead. This would increase the lipophilicity of the molecule (clogP values of 2.71 and 3.23 for keto-alkene **18** and **71** respectively), while keeping the essential parts of the molecule (tether and double bond) unchanged.

Entry	Compound	clogP value
1	cyclohexene	2.58
2	**1**	1.83
3	**18** and **19**	2.71
4	**28**	3.23
5	**30**	3.76

(Table 32: clogP values for Keto-alkenes)



70 **71**

Reagents and Conditions: (i), hexyne, BuLi, CuI, TMSI, Et_2O, -78°C, 14%; (ii), Lindlar catalyst, hydrogen, hexane, 57%.

(Scheme 52)

Keto-alkene **71** was submitted to the biphasic epoxidation conditions in the presence of Bu_4NHSO_4, and after 24 hrs the conversion to epoxide was found to be 8% by GC analysis. By increasing the propyl group to a butyl group the conversion of keto-alkene had thus dropped dramatically from 100% to 8%. This seems to indicate that ketone lipophilicity does play an important role in the epoxidation of keto-alkenes in the biphasic system. The effect of lipophilicity was investigated further by studying the intermolecular epoxidation reaction of cyclohexene, promoted by a series of ketones of increasing lipophilicity. The results of this study are displayed in Table 33. As can be seen, the epoxidation of cyclohexene drops dramatically from 44% with acetone to 14% with 2-butanone, and further drops to 4% with 2-hexanone. The decrease in conversion in going from acetone to 2-butanone may be partly explained by the fact that 2-butanone possesses α-substitution, making the carbonyl more sterically hindered. It does seem, though, that

the lipophilicity of the ketone plays an important role in the epoxidation of alkenes in this system.

Entry	Ketone	clogP[a]	Conv.[b] (% at 1 hr.)
1	acetone	-0.286	44
2	2-butanone	0.241	14
3	2-hexanone	1.295	4

Cyclohexene (2.5 mmol) in CH_2Cl_2 (25 cm^3), ketone (25 mmol), Bu_4NHSO_4 (0.5 mmol) and 1M $NaHCO_3$ (9 cm^3) was used in all the reactions reported in Table 33, which were run at 0°C. Oxone® was added as a 0.4M solution with $EDTANa_2$ (10 mg) in one portion. a) calculated using the hydrophobic fragmental constant approach. b) As measured by GC analysis.

(Table 33: The effect of Increasing Ketone Lipophilicity on the Epoxidation of Cyclohexene)

These results suggest that the water solubility of the ketone used in the epoxidation reaction is of critical importance. Further evidence against the epoxidation occurring in the organic phase came from our studies on a one phase CH_2Cl_2 system using Bu_4NHSO_5 as the organic soluble oxidant. Tetra-butylammonium Oxone® (TBA-Ox) is the expected form that the oxidant will take in the organic phase, when Bu_4NHSO_4 is used as the phase transfer catalyst in the biphasic system. Indeed, TBA-Ox has been shown to be an organic soluble oxidant[91] for the conversion of sulfides to sulfoxides and sulfones. The ability of TBA-Ox to epoxidise alkenes in the presence of a ketone in a one phase CH_2Cl_2 system was examined. TBA-Ox was prepared according to the procedure of Trost.[91] This involved stirring equal amounts of Bu_4NHSO_4 with Oxone® in water and extracting with CH_2Cl_2. Evaporation of the solvent yielded a white solid. This solid was titrated for oxidising ability and was found to contain 45% oxidant. TBA-Ox was used in several attempts to epoxidise both cyclohexene and keto-alkene **1** under a variety of one phase conditions (Table 34).

Entry	Alkene (mmol)	CH_2Cl_2 (cm^3)	TBA-Ox (mmol)	Na_2CO_3 (mmol)	Acetone (mmol)	Conv.[a] (%)
1	 5	50	7.5	none	none	0
2	 5	50	7.5	none	5	0
3	 5	50	7.5	7.5	5	0
4	**1** 0.36	5	0.54	none	none	0
5	**1** 0.36	5	0.54	0.54	none	0

a) As measured by GC analysis.

(Table 34: Attempted Epoxidation of Alkenes with TBA-Ox)

As can be seen in Table 34, TBA-Ox is incapable of epoxidising alkenes even in the presence of a ketone and base. This implies that under the biphasic conditions, TBA-Ox is not the active oxidant in the organic phase. If TBA-Ox is not the active oxidant in the organic phase, the other possibility is that Oxone® is the oxidant and the oxidation occurs in the aqueous phase.

These new ideas immediately provided an alternative explanation for the lack of ^{18}O label transfer in the "intramolecular" epoxidation of keto-alkene **1a**. If the keto-alkene must enter the aqueous phase, epoxidation in this system could well be due to direct background attack of the Oxone® on the double bond of the keto-alkene. It is puzzling then as to why 4-*tert*-butylcyclohexanone accelerated the reaction; after all, it is very lipophilic (clogP of 2.91). Bearing in mind that the alkene employed, cyclohexene, is quite hydrophilic, the acceleration seen by addition of 4-*tert*-butylcyclohexanone to the

reaction mixture could be due to the ketone acting as a co-solvent, solubilising the alkene to a greater extent in the aqueous phase. The nature of this effect is unknown and difficult to rationalise given the small amount of 4-*tert*-butylcyclohexanone present in the reaction. The ^{18}O labelling experiment was repeated using cyclohexanone, a ketone less lipophilic than 4-*tert*-butylcyclohexanone and conformationally unbiased, to see whether this would result in label transfer.

Cyclohexanone was ^{18}O labelled in a manner identical to that used previously to prepare ^{18}O label 4-*tert*-butylcyclohexanone and keto-alkene **1**. Mass spectrometry indicated that the ^{18}O label was incorporated in cyclohexanone to an extent of 83% (*m/z* = 100). This ^{18}O labelled cyclohexanone was used as a promoter in the biphasic epoxidation system, and after 5 hrs the reaction was found to be 20% complete by GC analysis. This higher conversion is probably due to cyclohexanone being more hydrophilic than 4-*tert*-butylcyclohexanone (which gave 15% conversion). Mass spectrometry of the product epoxide revealed that it was ^{18}O enriched by 12%, the rest of the ^{18}O label remaining intact in the carbonyl group. As only one oxygen of a dioxirane would be ^{18}O labelled, and assuming negligible kinetic isotope effect, epoxidation *via* a dioxirane would generate an equal amount of unlabelled epoxide and labelled epoxide. If the epoxidation process was mediated solely by a dioxirane, then a ketone with 83% ^{18}O label incorporation should yield an epoxide enriched with ^{18}O by 41%. This is not what was found; instead, ^{18}O label was incorporated in the epoxide to an extent of 12%. This implies that only 24% of the product epoxide was generated from a dioxirane intermediate. Thus it seems that the ketone is accelerating the reaction by more than one mechanism. The remaining 76% of epoxide must either be generated from a tetrahedral intermediate similar to **69**, or by the direct attack of Oxone® on the alkene. Whatever the non-dioxirane process is, it competes with epoxidation by a dioxirane. The level of epoxidation by each process seems to be dependent on the nature of the ketone used to promote the reaction.

In an interesting ^{18}O labelling experiment on his ketone (**61**), Denmark has recently shown[92] that in his case the epoxidation of his test alkene was due entirely to the action of a dioxirane. The experiment involved washing the ^{18}O label into the ketone under the

reaction conditions by use of $H_2{}^{18}O$. It was found that this was a rapid process and the amount of label incorporation in **61** was constant over time at 23%. After quantitative conversion of the test alkene to its epoxide under his previously described conditions,[20] the ^{18}O label enrichment of the epoxide was found to be 10%. This was calculated to be the level of enrichment expected for a dioxirane mediated process.

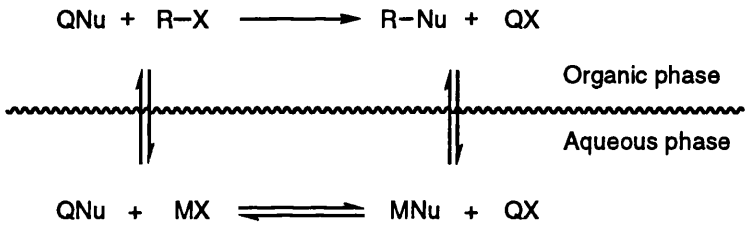
The results described above indicate that for simple aliphatic ketones there are at least two epoxidation processes involved. One is epoxidation by a dioxirane, and for the usually employed aliphatic ketones this appears to be the minor process. The other process, the major one in the case of the ketones we have studied, is undefined, but may involve a tetrahedral intermediate[85] or the ketone acting as a co-solvent, helping to solubilise the alkene in the aqueous phase where direct epoxidation by Oxone® on the alkene can occur. It is hoped that this work will encourage further studies into elucidating the nature of the oxidant responsible for alkene epoxidation in this system, though these studies were beyond the scope of this project.

4.1iii: The Role of the Quaternary Ammonium Salt

If the oxidation of the ketone occurs in the aqueous phase, then what is the role of the quaternary ammonium salt? It would seem that Bu_4NHSO_4 does not act to take the HSO_5^- into the organic phase, but it does have a dramatic effect on the outcome of the biphasic epoxidation of keto-alkene **1** (Table 26). In the biphasic system the absence of Bu_4NHSO_4 leads to 85% conversion and a *syn* / *anti* ratio of 3.5 : 1 (entry 7, Table 26). When Bu_4NHSO_4 is included in the reaction not only does the conversion increase to 100%, a ratio change to the formation of only the *syn* keto-epoxide **7a** is observed (entry 5, Table 26). It was initially thought that the quaternary ammonium salt was acting as a phase transfer catalyst. Indeed, tetra-butylammonium salts have commonly been used for phase transfer catalysis. Over the years phase transfer catalysis has received much attention,[93] and so a brief discussion of its principles and mechanism will be presented.

Phase transfer catalysis involving a quaternary ammonium salt generally involves two immiscible phases, usually an organic phase and an aqueous phase. The aqueous phase

contains the salt which will act as either a base or a nucleophile, while the organic phase contains the compound to be acted upon by the base or nucleophile. Because the compounds are in two different phases, no reaction can occur. When a quaternary ammonium salt is added as a phase transfer catalyst this situation changes. The lipophilic quaternary ammonium cation is soluble in both the aqueous and organic phases of the reaction. When in the aqueous phase, the quaternary ammonium group can exchange counterions with the excess of reagent anion present in that phase. The reagent, now paired with an organic soluble counter ion, can pass into the organic phase where it can undergo reaction with the organic soluble substrate. The quaternary ammonium cation can now return with an anion back into the aqueous phase for the process to be repeated (Figure 22).



(Figure 22)

A number of observations characteristic of quaternary ammonium salt mediated phase transfer catalysed reactions have been reported. In a study on the reaction of cyanide anion with *n*-octyl bromide, Starks found[94] that:

i) the reaction occurred in the organic phase.

ii) the rate of the reaction was directly proportional to the concentration of phase transfer catalyst.

iii) the reaction rate was independent of stirring rate, beyond a minimum rate that ensured effective mixing of the phases.

Herriott and Picker[95] studied the effect of the size of the alkyl groups on the rate of the reaction of thiophenolate substitution of *n*-octyl bromide. They showed that:

i) in general larger quaternary ammonium ions (entry 6, Table 35) are more effective than smaller ones (entry 1, Table 35) at phase transfer catalysis.

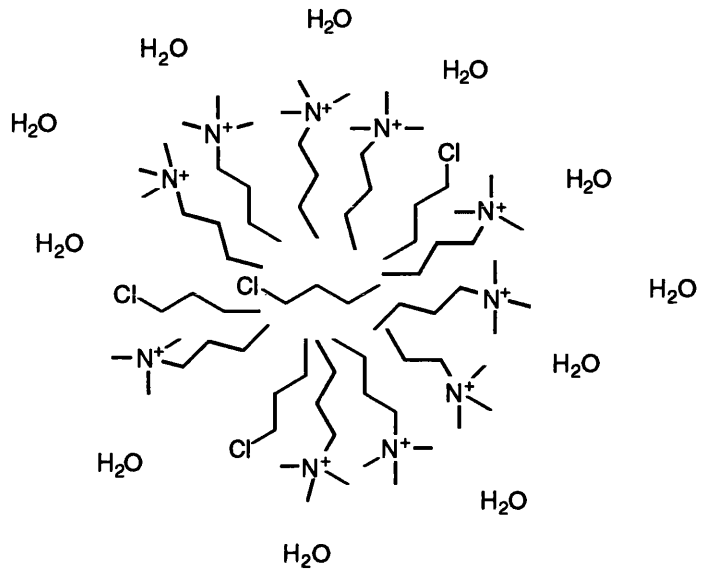
ii) a quaternary ammonium salt with three long chains is more effective at phase transfer catalysis (entry 5, Table 35) than a quaternary ammonium salt with only one long chain (entry 6, Table 35).

Entry	Catalyst	Relative rate
1	$(CH_3)_4NBr$	$< 2.2 \times 10^{-4}$
2	$(C_3H_7)_4NBr$	7.2×10^{-4}
3	$(C_4H_9)_4NBr$	0.70
4	$(C_4H_9)_4NI$	1
5	$(C_8H_{17})_3NCH_3Br$	4.2
6	$C_{16}H_{33}N(CH_3)_3NBr$	0.02

(Table 35: Relative rates of quaternary ammonium salt catalysed thiophenolate substitution of *n*-octyl bromide)

Besides acting as a phase transfer catalyst, quaternary ammonium salts have also been shown to act as surfactants, increasing the solubility of the organic substrate in the aqueous phase.[96] Biphasic reactions promoted by surfactants are fundamentally different to phase transfer catalysed reactions, so a brief discussion of surfactant promoted reactions will be presented. When added to a two phase organic / aqueous system, quaternary ammonium salt surfactants normally produce micelles. These micelles usually take the form of small aggregations of ~10 to 50 organic molecules dispersed in the aqueous phase. These molecules are arranged so the non-polar organic part of the surfactant and any other non-polar organic molecule occupy the internal hydrophobic

volume of the micelle, while the highly polar groups of the surfactant are oriented outward into the polar aqueous medium (Figure 23).



(Figure 23)

Micellar catalysis occurs when the positively charged outer surface of the micelle attracts and concentrates the inorganic anions from the bulk aqueous solution. This greatly facilitates the reaction of the concentrated anion with the organic compound within the micelle. The kinetics and mechanism of micelle catalysed reactions have been studied in recent years,[96-99] but are too complicated to be discussed here in any detail. In micelle catalysed and surfactant-promoted reactions, the quaternary ammonium salt takes the organic molecule into the aqueous phase. It is therefore valid to consider that the reaction takes place not in the organic phase, but in the aqueous phase. The rate of a micelle catalysed reaction does not increase in direct proportion to the amount of quaternary ammonium salt. Rather, the rate of the reaction increases slowly until the critical micelle concentration (cmc) is reached. At this point the rate of the reaction is dramatically increased, sometimes by as much as the sixth power of surfactant concentration. Increasing the amount of surfactant past the cmc does not further increase the rate of the reaction, and in some cases the rate may even decrease.

The cmc of a surfactant is dependent upon many variables such as the hydrophobicity of the hydrocarbon chains, the net charge on the surfactant, the nature of the polar head

groups, the counter ion, the temperature and pressure and additives in the biphase, so it is not an easy value to estimate. At this point it is appropriate to summarise the differences between phase transfer catalysed and micelle catalysed reactions, and see how they relate to the intramolecular biphasic epoxidation reaction. The following points were made in an excellent monograph by Starks:[100]

i) Quaternary ammonium salts that are good phase transfer catalysts are not always good surfactants. Small quaternary ammonium salts (like Bu_4NX) and large ones (like $(C_{12}H_{25})_4NX$) are both poor surfactants but are both good phase transfer catalysts. Good surfactants such as $C_{16}H_{33}NMe_3X$ are not always good phase transfer catalysts. In general a quaternary ammonium salt containing all alkyl groups the same length is a good phase transfer catalyst but a poor surfactant. A quaternary ammonium salt that contains one or two long chains and three or two short alkyl chains are good surfactants and poor phase transfer catalysts. It is interesting that there is evidence for this effect in Denmark's study on the oxopiperidinium salts that were used to catalyse the biphasic epoxidation reaction.[20] He was unable to explain why **61** with a $C_{12}H_{25}$ chain and a methyl group was a far superior promoter of the reaction to **62** which contains two hexyl chains.

ii) Phase transfer catalysed reactions take the inorganic reactant into the organic phase, while surfactants take the organic molecule into the aqueous phase. It has already been shown that the lipophilicity of the keto-alkenes has a significant effect on the rate of the intramolecular reaction. This indicates that the reaction occurs in the aqueous phase, and supports the idea that Bu_4NHSO_4 acts as a surfactant.

iii) The rate of phase transfer catalysis increases linearly with the concentration of quaternary ammonium salt. In systems where micellar catalysis is important, the rate of the reaction stays constant until the critical micelle concentration is reached. At this point there is a rapid acceleration in the rate of the reaction. Increasing the amount of quaternary ammonium salt past this concentration has little effect on the rate of the reaction. In the biphasic ketone - Oxone® epoxidation system it has been noticed, by Denmark, that

increasing the amount of quaternary ammonium salt does not increase the rate of the reaction as would be expected for a phase transfer catalysed process.[20] This effect was investigated by comparing the rates of three epoxidation reactions of cyclohexene to cyclohexene oxide under our conditions. One reaction contained no Bu_4NHSO_4, another contained 1 mmol of Bu_4NHSO_4 and a third reaction contained 5 mmols of Bu_4NHSO_4. The reactions were followed by GC and after 5 hrs it was found that the reaction with no Bu_4NHSO_4 contained 6% cyclohexene oxide. The reactions with 1 mmol and 5 mmol of Bu_4NHSO_4 contained identical amounts of cyclohexene oxide (16%) (Table 36). If the results concerning the effect of Bu_4NHSO_4 on the biphasic epoxidation system are compared to what has been discussed about the nature of phase transfer catalysis, it can be seen that there are several differences. One of these differences is that as the concentration of Bu_4NHSO_4 increases there is no parallel increase in the rate of the epoxidation reaction (entries 2 and 3, Table 36). Although our results are only qualitative, if the role of the quaternary ammonium salt was as a phase transfer catalyst then an increase in the rate of the reaction would have been expected. These results imply that Bu_4NHSO_4 acts not as a phase transfer catalyst, but as a surfactant.

Entry	Amount of TBAHS (mmol)	Conv. at 5 hrs. (%)[a]
1	none	6
2	1	16
3	5	16

Cyclohexene (5 mmol) in CH_2Cl_2 (50 cm^3), acetone (5 mmol) and 1M $NaHCO_3$ (17 cm^3) was used in all the reactions reported in Table 36, which were run at 0°C. Oxone® was added as a 0.4M solution with $EDTANa_2$ (20 mg) in one portion. [a] As measured by GC analysis.

(Table 36: Effect of Increasing the Amount of Bu_4NHSO_4 on the Biphasic Epoxidation of Cyclohexene)

iv) Small changes in the types of ion present in solution can dramatically affect the ability of a quaternary ammonium salt to act as a phase transfer catalyst or a surfactant. This effect can been seen in the work of Denmark (Table 25). Ketone **61** is a very efficient

promoter of the epoxidation reaction, but when the counter ion is changed from triflate to nitrate (ketone **64**) the conversion almost halves over a similar time period.

The theory of Bu_4NHSO_4 acting as a surfactant was tested using the intermolecular system and a phase transfer catalyst that is unable to act as a surfactant (18-crown-6). If the reaction proceeded *via* phase transfer catalysis, then the reaction containing 18-crown-6 and acetone should be just as fast as the one containing Bu_4NHSO_4 and acetone. If, however, surfactant effects were important, then the rate of the reaction with 18-crown-6 and acetone would be slower than the rate of the reaction that contained acetone and Bu_4NHSO_4, but the same as the rate of the reaction that contained only acetone. All the experiments used the $NaHCO_3$ buffered conditions that have been detailed earlier in this thesis. The amount of phase transfer agent (either Bu_4NHSO_4 or 18-crown-6) was 1 mmol, the reactions were run for 5 hrs and the conversions monitored by GC analysis. The results of these experiments are displayed in Table 37.

Entry	Catalyst	acetone (mmol)	Conversion[a] (%)
1	Bu_4NHSO_4	none	2.5
2	none	5	6
3	Bu_4NHSO_4	5	16
4	18-crown-6	5	8
5	Bu_4NHSO_4	50	44
6	none	50	33

Cyclohexene (5 mmol) in CH_2Cl_2 (50 cm^3) and 1M $NaHCO_3$ (17 cm^3) was used in all the reactions reported in Table 37, which were run at 0°C. Oxone® was added as a 0.4M solution with $EDTANa_2$ (20 mg) in one portion. [a)] As measured by GC analysis.

(Table 37: The Effect of Changing the Phase Transfer Catalyst on the Biphasic Epoxidation of Cyclohexene)

As can be seen, entries 2 and 4 have similar conversions after 5 hrs. Entry 3, the reaction run with Bu_4NHSO_4, shows an increased conversion. The conversions with only 1 equiv. of acetone were low, so the reactions were repeated with 10 equiv. of

acetone present (entries 5 and 6). The conversions in these experiments were higher, and the effect of the quaternary ammonium salt can still be seen. This supports the idea that it is the role of Bu_4NHSO_4 to act as a surfactant and take the ketone into the aqueous phase. Once in the aqueous phase the ketone can be attacked by caroate to form a dioxirane (and tetrahedral intermediate?), which can then be taken by Bu_4NHSO_4 back into the organic phase where it can epoxidise the alkene. It is interesting to note at this point, that in his original work, Curci often employed 18-crown-6 as a phase transfer catalyst.[5, 13] He did not, however, report the results of the experiment without 18-crown-6 but with acetone, so it is probable that the accelerations seen are due entirely to the excess of acetone present in his system.

The overall picture now, then, was that the ketone must go into the aqueous phase to be oxidised by Oxone® to the intermediate responsible for alkene epoxidation. The role of the quaternary ammonium salt is to act as a surfactant to help take the ketone into the aqueous phase. These results raised the question of using a better surfactant to promote the reaction. It should be noted that while this may well increase the rate of epoxidation, this could well be due to the surfactant solubilising the alkene in the aqueous phase as well as the ketone, which would lead to direct epoxidation by Oxone®. It is this process of direct epoxidation by Oxone® that must be avoided if an asymmetric variation of this system is to be developed. In the intramolecular system, where the alkene and the ketone are in the same molecule anyway, this process is not problematic. It was decided to see whether the rate of the epoxidation of keto-alkene **1** could be enhanced by the use of a quaternary ammonium salt known to be a better surfactant. $C_{16}H_{33}N(CH_3)_3NHSO_4$ is such a quaternary ammonium salt, so keto-alkene **1** was epoxidised under the biphasic conditions, but this time using $C_{16}H_{33}N(CH_3)_3NHSO_4$ as the quaternary ammonium salt instead of Bu_4NHSO_4. The reaction conditions were identical to those in entry 4, Table 26, except that the $NaHCO_3$ buffering system was used and the results are displayed in Table 38.

Entry	Quaternary ammonium salt	Conversion (% at 8 hrs)[a]
1	Bu_4NHSO_4	27
2	$C_{16}H_{33}N(CH_3)_3NHSO_4$	20

Keto-alkene **1** (50 mg, 0.36 mmol) in CH_2Cl_2 (5 cm^3), Oxone® (14.9 mmol) as a 0.48M solution with $EDTANa_2$ (12.5 mg) and 1M $NaHCO_3$ (22 cm^3) was used in all the epoxidation reactions reported in Table 38. [a] As measured by GC.

(Table 38: Effect of Changing Quaternary ammonium salt in the Intramolecular Epoxidation Reaction)

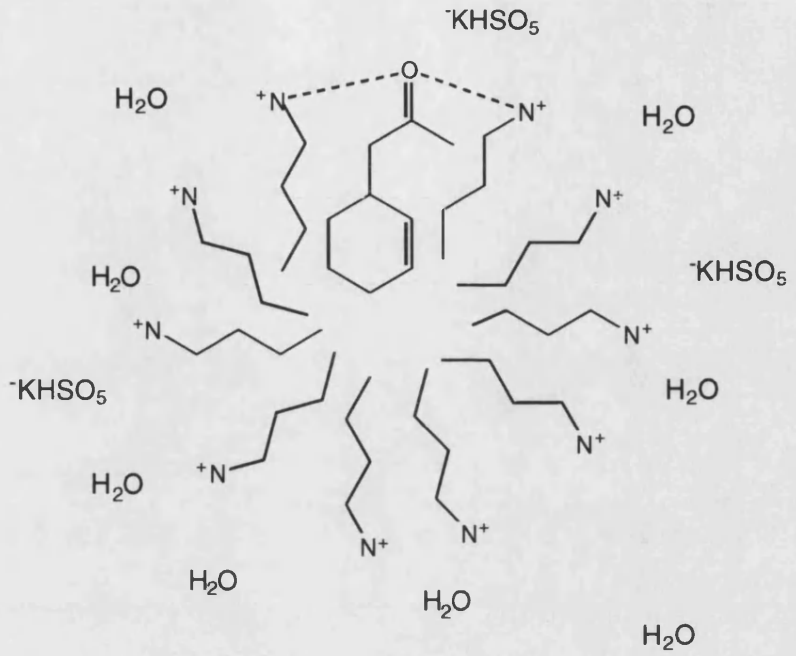
Surprisingly, the expected acceleration was not observed. Instead a slight decrease in the conversion was noted. Two possible explanations can be advanced. One possibility is that Bu_4NHSO_4, with its relatively short alkyl chains, may well form micelles of a size more accommodating to keto-alkene **1** than the much bigger micelle that would be expected to be formed with the longer alkyl chain present in $C_{16}H_{33}N(CH_3)_3NHSO_4$. Alternatively, the critical micelle concentration for $C_{16}H_{33}N(CH_3)_3NHSO_4$ may not have been reached. To really understand what processes are taking place a full physical organic chemistry study of the system is required. This study is beyond the scope of the work detailed in this thesis, but we believe that the qualitative results detailed here provide some explanation as to the basic nature of some of those processes.

A question remains unanswered: why is there a ratio change in the biphasic epoxidation of keto-alkene **1** when a quaternary ammonium salt is introduced (entries 4 and 6, Table 26)? There are at least two possibilities:

(i) With a quaternary ammonium salt present, the epoxidation is still due to direct Oxone® attack, but now occurs inside a micelle instead of in the bulk aqueous phase. This change in environment could cause the ratio change.

(ii) The carbonyl oxygen in some way interacts with the charged ammonium groups at the micelle / water interface (Figure 24). This could result in the alkene being buried within the micelle and so be protected from direct attack by Oxone®. Attack by Oxone® would then have to occur at the carbonyl group, which could generate a tetrahedral

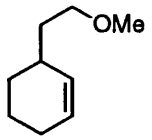
intermediate capable of epoxidation of the alkene within the micelle. This intramolecular epoxidation by a tetrahedral intermediate could be responsible for the ratio change.



(Figure 24)

These possibilities are difficult to test but some recent work in these laboratories provides relevant information. This work involved the study of methyl ether **72** (Figure 25), which has approximately the same lipophilicity as keto-alkene **1** and could form a similar micelle to the one proposed above. Methyl ether **72** was submitted to the biphasic conditions with and without Bu_4NHSO_4. For completeness, a brief summary of the results will be presented here; they will be detailed in full elsewhere.[101] The idea was that if the ratio change was due to the micellar environment then different ratios in the epoxidation of methyl ether **72** should occur when the reaction is carried out in the presence and absence of Bu_4NHSO_4. If the change in ratio is in some way related to the presence of the carbonyl group, then no ratio change should occur. When methyl ether **72** was submitted to the reaction with and without Bu_4NHSO_4 present, the ratio of diastereomeric epoxides was the same in both cases, 1:1. This implies that the carbonyl group in keto-alkene **1** may be in some way involved in its diastereoselective epoxidation.

Unfortunately, this carbonyl involvement does not help the diastereoselectivity in the epoxidation of the acyclic systems.



72

(Figure 25)

4.2: Conclusions

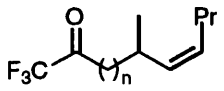
Our work has shown that the ketone-accelerated biphasic epoxidation of alkenes by Oxone® is a complex system. While our results are qualitative and a full mechanistic study was not in the scope of this project, we believe that we have evidence for the following:

(i) The oxidation of the ketone occurs in the aqueous phase. This is supported by the decrease in conversion of the alkene to epoxide in both the intra- and intermolecular systems the more lipophilic the ketone becomes. A second piece of evidence, that TBA-Ox does not oxidise either ketones or alkenes in a one phase CH_2Cl_2 system, also supports this.

(ii) The role of the quaternary ammonium salt is to act as a weak surfactant, helping to take the ketone into the aqueous phase to be oxidised. This is shown by the results in Table 37, where the phase transfer catalyst 18-crown-6 was shown to have no effect on the conversion, whereas Bu_4NHSO_4, which can act as a surfactant, almost doubled the conversion. These results have several consequences for both the intra- and intermolecular reactions, and these will be discussed in turn.

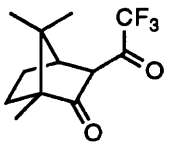
In the intramolecular reaction the ketone and the alkene are in the same molecule. Therefore both functionalities are taken into the aqueous phase. This means that any

ketone mediated process must compete with direct background epoxidation by Oxone®. It is this, we believe, that accounts for the poor stereoselectivities in the acyclic systems. It may be possible to bias this system so as to increase the rate of attack at the carbonyl. This might be achieved by constructing molecules of the type shown in Figure 26. Here, the reactivity of the carbonyl has been increased by introduction of a trifluoromethyl group. It does seem, however, that a general intramolecular procedure for a wide range of keto-alkenes is unlikely to be successful.



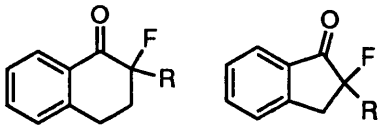
(Figure 26)

In light of the international activity in the area of chiral ketone design and synthesis, with the aim of performing ketone-catalysed intermolecular asymmetric epoxidation, it is worth commenting on how the results described in this thesis will effect that goal. The main challenge is to avoid background epoxidation. To do this, the alkenes used must not be water soluble to any significant degree. More importantly, however, a careful choice of ketone will need to be made. The ketone must be able to shuttle between phases, but must not solubilise the alkene in the aqueous phase. Our results can now explain the poor conversions and enantiomeric excesses reported by both Curci's[102] and Marples'[103] chiral ketones. In the case of Curci, ketones derived from camphor were used (Figure 27), but even after 48 hrs. of continuous addition of Oxone® (> 10 equiv. with respect to ketone) the yields were less than 80% and the enantiomeric excesses a disappointing 20% maximum.



(Figure 27)

Marples used substituted tetralones and indanones (Figure 28) for his study. He too found that vast excesses of Oxone®, up to 240 equivs., gave yields of 14-100%, depending on the alkene, over several days. However, these ketones failed to provide enantioenriched epoxide products. We believe that the poor conversions seen in these systems is at least partly due to the fact that the ketones are far too lipophilic to enter the aqueous phase to be oxidised by the Oxone®. Over extended periods of time, and with large excesses of Oxone®, direct epoxidation occurs resulting in low enantiomeric excesses.



R= alkyl, CO_2Pr, CO_2Me

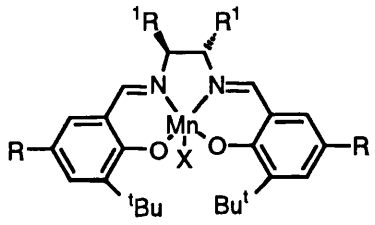
(Figure 28)

Considering the complex issues that will have to be considered and overcome, it is probably easier to examine Yang's homogeneous acetonitrile / water system mentioned earlier.[17, 18] This system, however, could only be used for the epoxidation of electron deficient alkenes like styrenes, stilbenes and chalones. This is due to the fact that these alkenes are not epoxidised directly by Oxone®; aliphatic alkenes such as cyclohexene do undergo rapid epoxidation by Oxone® under these conditions.[19] It would seem sensible to use the Yang system to test the structural characteristics of the ketone to see whether it is capable of promoting the reaction efficiently, and then if successful, use the ketone in the more general biphasic system.

4.3: Other Possible Reagents for Ketone Directed Intramolecular Epoxidation

With the failure of the intramolecular ketone - Oxone® biphasic system to be of use in the stereocontrolled epoxidation of keto-alkenes other than **1**, it was decided to investigate other methods of possible ketone directed intramolecular epoxidation. The methods to be

examined were those in which oxidants attacked carbonyl groups and not unfunctionalised alkene double bonds. Examples of these types of reactions are the Baeyer-Villiger oxidation, and nucleophilic epoxidation of enone double bonds. We reasoned that a nucleophilic oxidant might attack the carbonyl group and not the alkene, which could generate an intermediate capable of intramolecular alkene epoxidation. Jacobsen has recently reported an oxidation system that is unreactive to alkenes unless a (salen)$Mn^{(III)}$ complex is present.[104] Jacobsen found that a 1:1 mixture of *m*CPBA and NMO at -78°C in CH_2Cl_2 could oxidise the (salen)$Mn^{(III)}$ complex (Figure 29) to a species capable of alkene oxidation. Jacobsen has shown that the *m*CPBA / NMO formed a complex that although able to oxidise the (salen)$Mn^{(III)}$ complex was unable to oxidise alkenes directly. Consequently unfunctionalised alkenes were oxidised with good to excellent enantioselectivities.

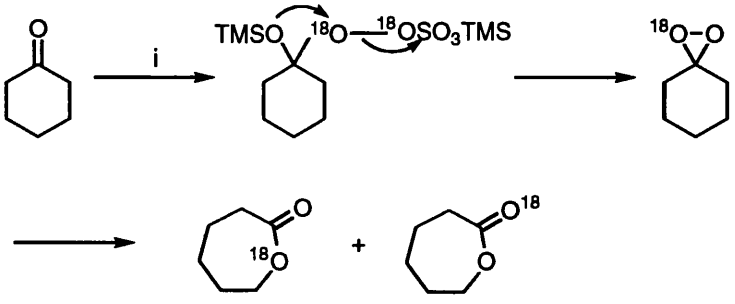


X is -Cl, or on oxidation =O

(Figure 29)

As the *m*CPBA / NMO complex does not epoxidise alkenes directly, it may be of use in a carbonyl directed intramolecular epoxidation system if it can add to a carbonyl group like *m*CPBA does in the first step of the Baeyer-Villiger reaction. This system was employed in an attempt to epoxidise keto-alkene **1**, but even at elevated temperatures no epoxidation occurred. To discover whether the *m*CPBA / NMO complex is capable of oxidising ketones to esters *via* a Baeyer-Villiger oxidation reaction, acetophenone was treated with the *m*CPBA / NMO reagent. However, even after 24 hrs no ester product was formed. It seems that while being able to oxidise the (salen)$Mn^{(III)}$ complex the *m*CPBA / NMO system is unable to oxidise ketones.

The ability of oxidants to add to a ketone carbonyl group in the Baeyer-Villiger reaction prompted an investigation of other reagents which have been used for this purpose. If an oxidant can add to the carbonyl group of keto-alkene **1**, then since **1** has groups of low migratory aptitude, an intramolecular epoxidation reaction may occur faster than the Baeyer-Villiger reaction, resulting in a ketone directed intramolecular epoxidation reaction. One such reagent that is known to oxidise ketones to esters, in fact *via* a dioxirane intermediate, is TMS-Oxone®.[105] It has been shown by Curci in ^{18}O labelling experiments with doubly ^{18}O labelled TMS-Oxone® that a dioxirane intermediate is involved in the oxidation reactions of cyclohexanone to γ-caprolactone and acetophenone to phenyl acetate and methyl benzoate.[105] If a dioxirane intermediate is involved then the dioxirane formed should have 50% label incorporation, which should lead to ester formation with scrambling of the ^{18}O label (Scheme 53). Indeed, ^{18}O label was found to be present in both the carbonyl and ester oxygens. If the conventionally proposed tetrahedral intermediate was the immediate precursor to the ester then the ^{18}O label would be expected to reside exclusively in the ester oxygen. TMS-Oxone® can be prepared by the action of sulfur trioxide on bis(TMS) peroxide. On treatment of keto-alkene **1** with a freshly prepared solution of TMS-Oxone®, no recognisable products could be isolated. This is probably due to the strongly Lewis acidic nature of TMS-Oxone, which has been shown to cause the decomposition of epoxides.[105]



Reagents and Conditions: (i),TMS-Oxone®, CH_2Cl_2.

(Scheme 53)

The next group of reactions investigated were those oxidation systems that are known to epoxidise enone double bonds. It was reasoned that in the case of keto-alkene **1**

nucleophilic attack should occur at the carbonyl group, which may well generate a species capable of alkene epoxidation. The two systems looked at were TBHP / BuLi / THF[106] and NaOH / H_2O_2 / MeOH,[107, 108] both of which have been used to epoxidise enones. However, these systems failed to generate any products whatsoever, and in both cases keto-alkene **1** was recovered. Other systems that may generate nucleophilic oxidants were also investigated (Table 39), but these too failed to yield any epoxide.

As mentioned previously in this thesis, α-hydroxy peroxyesters have been used in the epoxidation of simple alkenes. In the same paper[64] ketals were shown to be able to epoxidise unfunctionalised alkenes when treated with 90% H_2O_2, presumably by the formation *in situ* of a α-methoxy peroxy ether. The dimethyl ketal **8** was treated with H_2O_2, but even after heating to reflux no epoxidation occurred. Table 39 summarises the various systems that were investigated in an attempt to find conditions that would generate a stereoselective ketone directed epoxidation reaction.

Entry	Reaction Conditions	Result
1	*m*CPBA, NMO, CH_2Cl_2	No reaction
2	*m*CPBA, NMO, CH_2Cl_2, heat	No reaction
3	TMS-Oxone®, CH_2Cl_2	No isolable products
4	TBHP, BuLi, THF	No reaction
5	NaOH, H_2O_2, MeOH	No reaction
6	DBU, TBHP, THF	No reaction
7	DBU, TBHP, THF, reflux	No reaction
8	TBHP, NaOH, MeOH	No reaction
9	*m*CPBA, NaOH, MeOH	No reaction
10	*m*CPBA, BuLi, THF	No reaction
11	ketal **8**, H_2O_2, THF	No reaction
12	ketal **8**, H_2O_2, THF, reflux	No reaction

(Table 39: Other Epoxidation Systems Investigated)

Even though a variety of nucleophilic oxidising reagents was examined, we were unable to find any that could effect the ketone directed intramolecular epoxidation of an acyclic alkene double bond.

Chapter 5:

Conclusions

5.1: Overall Conclusions

In the course of conducting the work that is presented in this thesis, many surprising discoveries have been made on the nature of ketone directed epoxidation processes. We have shown that peracid and DMDO epoxidation of cyclic keto-alkenes similar to **1** can be directed by the ketone carbonyl. In the case of the DMDO epoxidation reaction, the carbonyl groups of esters and amides were also shown to be able to direct the epoxidation reaction. We have suggested that the directing effect of ketones in the peracid epoxidation may be due to intramolecular epoxidation by a tetrahedral intermediate, formed by the attack of the peracid on the carbonyl group of the ketone. In the case of the directed DMDO reactions, our results have been tentatively rationalised by a suggestion of an interaction between the dipoles of the carbonyl group and DMDO. Of course, this may also be the case for the selectivity in the peracid epoxidation of the same keto-alkenes. The peracid and DMDO methodology could not be extended to any acyclic keto-alkenes, due to the faster rate of the direct intermolecular background epoxidation.

It was hoped that the biphasic ketone-Oxone® system would enable us to investigate intramolecular dioxirane epoxidation without a rapid intermolecular background Oxone® reaction. In the course of these investigations we were able to show that the generally accepted mechanism for epoxidation in this ketone-Oxone® system was incorrect. Firstly, oxidation of the ketone occurs in the aqueous phase and not in the organic phase as was originally thought. Secondly, again contrary to what was previously believed, the quaternary ammonium salt does not act as a phase transfer catalyst. The quaternary ammonium salt does not take Oxone® into the organic phase, but it does act as a weak surfactant taking the ketone into the aqueous phase. As well as having practical consequences, it is hoped that these results will stimulate further study into the precise mechanism of the biphasic, ketone-accelerated Oxone® epoxidation of alkenes.

Chapter 6:

Experimental

6.1: Experimental

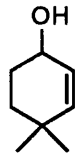
6.1i: General

All NMR spectra were recorded in $CDCl_3$ on a Jeol GX 270, Jeol EX 400, Bruker AM 300 or Varian Unity 300 spectrometer. *J* values are given in Hz and are quoted as stated in the relevant peak print outs. *No effort has been made to correct for discrepancies in the peak print out values.* Multiplicities in ^{13}C spectra were determined by DEPT experiments. IR spectra were recorded on a Perkin-Elmer 1605 FT-IR spectrometer. Mass spectra were recorded under EI conditions unless otherwise stated. EI and CI (isobutane) spectra were recorded on VG 7070B, VG 12-253 or VG ZAB-E instruments. FAB spectra (from *meta*-nitrobenzyl alcohol) were recorded on a VG AutoSpec machine. All GC analysis was performed using a GC / MS (Fisons MD-800; DD-1 25 m x 0.25 mm column, film thickness 0.25 μm; 10 minutes at 30°C, ramp at 20°C per minute to 150°C, held at 150°C for 30 minutes.

Microanalyses were performed in the School of Chemistry, University of Bath. Diethyl ether (referred to throughout as ether) and THF were distilled from sodium-benzophenone ketyl; toluene from sodium; and dichloromethane from phosphorus pentoxide. Petrol refers to light petroleum b.p. 60-80 °C which was redistilled prior to use. All commercial reagents were used without further purification unless stated otherwise in the appropriate text. Flash column chromatography was performed using Matrex silica Si. Where appropriate, the silica was neutralised by flushing it once with a 1% solution of triethylamine in the appropriate eluent.

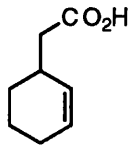
6.1ii: Experimental Procedures

4,4-dimethyl-2-cyclohexen-1-ol.



Sodium borohydride (610 mg, 16 mmol) was added portionwise to a stirred, ice cold solution of 4,4-dimethyl-2-cyclohexen-1-one (2.12 cm^3, 16 mmol) and cerium trichloride heptahydrate (5.9 g, 16 mmol) in methanol (40 cm^3). When the reaction was shown to be complete by TLC (40% EtOAc – petrol) it was quenched with saturated NH_4Cl solution and the volume was reduced *in vacuo*. The residue was acidified (2M HCl) and extracted three times with CH_2Cl_2, the combined organics being washed with brine and dried ($MgSO_4$). Purification by flash chromatography yielded 4,4-dimethyl-2-cyclohexen-1-ol (1.8 g, 89%), as an oil; ν_{max} /cm^{-1} 3415, 2953, 1646 and 1035; δ_H (270 MHz) 5.61-5.49 (2H, m), 4.14 (1H, m), 1.90 (1H, m), 1.67-1.51 (3H, m), 1.42 (1H, dd, *J* 9.9, 3.5), 1.01 (3H, s) and 0.96 (3H, s); δ_C (67.5 MHz) 140.6 (s), 132.6 (s), 127.3 (d), 65.8 (d), 33.6 (t), 31.8 (t), 29.2 (q) and 29.1 (q); *m/z* 126 (M^+), 111, 93, 70 and 55. (Found: M^+, 126.1040. $C_8H_{14}O$ requires M, 126.1045.)

2-Cyclohexen-1-acetic acid **3**.[110]

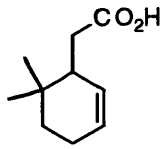


3

A solution of cyclohex-2-en-1-ol (5 g, 51 mmol) and propionic acid (1 cm^3) in triethyl orthoacetate (100 cm^3) was heated to 140°C for 16 hrs, any ethanol formed being distilled away from the reaction. The reaction mixture was then allowed to cool and diluted with ethyl acetate. The organics were washed successively with 2M HCl, saturated sodium

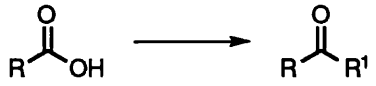
bicarbonate solution and brine, dried ($MgSO_4$) and evaporated, to yield a mixture of ethyl ester **2** and 2-acetoxycyclohexene (6.9 g) as an orange oil. 1M Sodium hydroxide solution (60 cm^3) was added to a stirred solution of this mixture (6.9 g) in methanol (60 cm^3). On completion, the reaction mixture was diluted with CH_2Cl_2 and washed with water. The organic layer was discarded. The aqueous layer was acidified with 1M HCl and extracted twice with CH_2Cl_2. The combined organics were dried ($MgSO_4$) and the solvent evaporated to yield the acid **3** (2.66 g, 37%) as a dark oil. (Found C, 68.5; H, 8.7. $C_8H_{12}O_2$ requires C, 68.6; H, 8.6%); ν_{max} (film) / cm^{-1} 2931, 2674, 1700, 1409, 1291, 1050, 957 and 725; δ_H (270 MHz) 5.73 (1H, m), 5.55 (1H, dd, *J* 10.0, 2.0), 2.60 (1H, m), 2.36-2.31 (2H, m), 2.00-1.48 (4H, m) and 1.36-1.13 (2H, m); δ_C (67.5 MHz) 178.9 (s), 129.8 (d), 128.4 (d), 40.5 (t), 32.1 (d), 28.8 (t), 24.9 (t) and 20.9 (t); *m/z* 140 (M^+), 122 (M^+-H_2O), 94 (M^+-H_2O-CO), 81 and 80.

6,6-dimethyl-2-cyclohexen-1-acetic acid (precursor of **10**).



Prepared in an identical manner to 2-cyclohexen-1-acetic acid **3**, except that 4,4-dimethyl-2-cyclohexen-1-ol was used as the starting material. Yield 44%. (Found C, 71.3; H, 9.71. $C_{10}H_{16}O_2$ requires C, 71.3; H, 9.58%); ν_{max} (film) / cm^{-1} 2919, 1707 and 1297; δ_H (300 MHz) 5.69-5.64 (1H, m), 5.52 (1H, dd, *J* 10.1, 1.7), 2.55 (1H, dd, *J* 15.0, 4.0), 2.39-2.33 (1H, m), 2.11-2.06 (1H, m), 2.03-2.01 (1H, m), 1.41 (2H, t, J 6.4), 0.98 (3H, s) and 0.81 (3H, s); δ_C (75 MHz) 179.6, 128.6, 126.8, 41.5, 35.4, 35.3, 31.11, 28.5, 22.8 and 21.9; *m/z* 168 (M^+), 153 (M^+- CH_3), 108, 93 and 77.

General Procedure for the Preparation of Ketones ***1***,[110] ***9***, ***10***, ***11*** *and* ***12*** *from the parent acid by alkyl lithium addition.*



A solution of the acid **3**, 6,6-dimethyl-2-cyclohexen-1-acetic acid or 2-cyclopenten-1-acetic acid (Aldrich) (1.85 mmol) in THF (15 cm^3) under nitrogen was treated rapidly with alkyl lithium (4 equivalents) at 0°C and the mixture left to stir. When the reaction was complete it was quenched with freshly distilled chlorotrimethylsilane (5 cm^3, 40 mmol) and allowed to warm to room temperature. 1M HCl (15 cm^3) was then added and the solution stirred for 20 minutes. The mixture was extracted three times with ether, the combined organics washed with water, dried (Na_2SO_4) and evaporated to yield a yellow oil. Flash chromatography (10% ether-petrol) gave the ketone.

1-[Cyclohex-2-enyl]-2-propanone **1**.— Yield 85%; ν_{max} /cm^{-1} 2910, 1720, 1350 and 1150; δ_H (400 MHz) 5.68 (1H, dq, *J* 10.0, 3.0), 5.47 (1H, ddd, *J* 10.1, 4.7, 2.3), 2.57 (1H, m), 2.42 (1H, dd, *J* 16.2, 6.7), 2.37 (1H, dd, *J* 16.2, 7.9), 2.21 (3H, s), 1.98-1.93 (2H, m), 1.78 (1H, m), 1.67 (1H, m), 1.53 (1H, m) and 1.19 (1H, m); δ_C (100 MHz) 208.1 (s), 130.0 (d), 127.8 (d), 49.9 (t), 31.0 (d), 30.3 (q), 28.8 (t), 24.9 (t) and 20.9 (t); *m/z* 138 (M^+), 95 (M^+-CH_3CO), 80 and 43. (Found: M^+, 138.1069. $C_9H_{14}O$ requires M, 138.1045.)

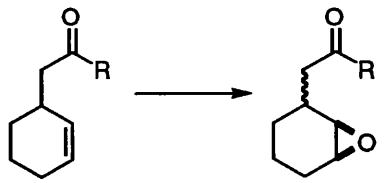
1-[Cyclohex-2-enyl]-5-methyl-hexan-2-one **9**.—Yield 54%; ν_{max} /cm^{-1} 2926, 2869, 1710, 1467, 1383, 1366, 1252, 1060 and 842; δ_H (400 MHz) 5.68 (1H, m), 5.48 (1H, m), 2.40-2.36 (2H, m), 1.96 (1H, m), 1.80-1.43 (6H, m), 1.26-1.12 (3H, m), 0.88 (3H, d, *J* 10.1) and 0.87 (3H, d, *J* 10.4); δ_C (100 MHz) 210.8 (s), 130.6 (d), 127.8 (d), 49.02 (t), 41.5 (t), 32.6 (t), 31.1 (d), 28.9 (t), 27.9 (d), 22.6 (t), 22.3 (q), 22.3 (q) and 21.0 (t); *m/z* 194 (M^+), 123 (M^+-^{i}amyl) and 81. (Found: M^+, 194.1667. $C_{13}H_{22}O$ requires M, 194.1671.)

1-[6,6-dimethylcyclohex-2-enyl]-2-propanone **10**.—Yield 70%; ν_{max} /cm^{-1} 2956, 2913, 1717, 1363 and 1163; δ_H (300 MHz) 5.63 (1H, m), 5.37 (1H, dq, *J* 10.1, 2.4), 2.55 (1H, dd, *J* 16.1, 3.7), 2.41 (1H, m), 2.18 (1H, m), 2.15 (3H, s), 2.02-1.96 (2H, m), 1.40 (2H, t, *J* 6.2), 0.94 (3H, s) and 0.78 (3H, s); δ_C (75 MHz) 209.0, 129.1, 126.3, 44.8, 40.4, 35.4, 31.0, 30.5, 28.5, 22.8 and 22.1; *m/z* 166 (M^+), 108 and 93. (Found: M^+, 166.1360. $C_{11}H_{18}O$ requires M, 166.1358.)

1-[Cyclopent-2-enyl]-5-methyl-hexan-2-one **11**.—Yield 64%; ν_{max} /cm^{-1} 2955, 1715, 1467, 1366 and 719; δ_H (400 MHz) 5.74 (1H, m), 5.62 (1H, m), 3.09 (1H, m), 2.49 (1H, dd, *J* 16.1, 6.8), 2.41 (1H, dd, *J* 14.7, 7.8), 2.32 (1H, m), 2.12 (1H, m), 1.56-1.50 (4H, m), 1.48-1.23 (3H, m) and 0.88 (6H, d, *J* 6.4); δ_C (100 MHz) 210.9 (s), 134.0 (d), 131.0 (d), 48.9 (t), 41.1 (d), 32.6 (t), 31.8 (t), 29.9 (t), 27.7 (t), 22.6 (d) and 22.3 (q); *m/z*180 (M^+), 109 (M^+-^{i}amyl), 81 and 67. (Found: M^+, 180.1490. $C_{12}H_{20}O$ requires M, 180.1514.)

1-[Cyclopent-2-enyl] -2-propanone **12**.—Yield 71%; ν_{max} /cm^{-1} 2951, 1710 and 1362; δ_H (270 MHz) 5.74 (1H, dq, *J* 5.7, 2.2), 5.62 (1H, m), 3.10 (1H, m), 2.52 (1H, dd, *J* 16.5, 6.8), 2.42 (1H, dd, *J* 16.5, 7.9), 2.36-2.05 (2H, m), 2.13 (3H, s) and 1.44-1.13 (2H, m). δ_C (100 MHz) 209.0 (s), 133.9 (d), 131.2 (d), 49.9 (t), 40.9 (d), 31.7 (t), 30.2 (q) and 29.8 (t); *m/z*: 124 (M^+), 123 (M^+-1), 108 (M^+-O). and 67. (Found: M^+, 124.0873. $C_8H_{12}O$ requires M, 124.0888.)

General Epoxidation Procedures



a) *with mCPBA*

A stirred solution of the alkene (0.34 mmol) in a mixture of CH_2Cl_2 (1 cm^3) and saturated aqueous sodium bicarbonate solution (1 cm^3) was treated portion wise with *m*CPBA (@ 50%, 0.68 mmol) under nitrogen. When the reaction was complete, water (4 cm^3) was added, followed by solid Na_2SO_3 (until no more O_2^{2-} was present, as indicated by Merck semi-quantitative peroxide papers). The mixture was diluted with ether and the organic layer separated, washed successively with saturated aqueous sodium bicarbonate solution and water, dried (Na_2SO_4) and evaporated to give the crude product.

1(1R, 2S*, 3R*)-1-[3-(1,2-epoxycyclohexanyl)]-2-propanone* **7a**.

Reaction of alkene **1** with *m*CPBA by the general procedure above, followed by flash chromatography (20% EtOAc – petrol) afforded the epoxide **7a** (61%) as a colourless oil; ν_{max} /cm^{-1} 2935, 1715, 1441, 1363, 1258, 1180 and 860; δ_H (270 MHz) 3.14 (1H, dt, *J* 4.0, 0.7), 3.08 (1H, dd, *J* 4.0, 2.3), 2.70 (1H, m), 2.50-2.30 (2H, m), 2.10 (3H, s) and 1.90-1.00 (6H, m); δ_C (67.5 MHz) 210 (s), 55.1 (d), 53.5 (d), 46.7 (t), 30.5 (d), 30.1 (q), 25.0 (t), 23.5 (t) and 19.3 (t); *m/z* (CI) 155 (MH^+), 137 (M-OH) and 97. (Found: MH^+, 154.0991. $C_9H_{14}O_2$ requires MH, 154.0994.)

1(1R, 2S*, 3R*)-1-[3-(1,2-epoxycyclohexanyl)]-5-methyl-2-hexanone* **13a**.

Reaction of alkene **9** with *m*CPBA by the general procedure above afforded a *ca.* 4:1 mixture of **13a** and **13c** according to ^1H NMR analysis of the crude reaction mixture

(peaks for **13c** at *ca.* 3.6 ppm). Flash chromatography (20% EtOAc – petrol) afforded the epoxide **13a** (45%) as a colourless oil; ν_{max} /cm^{-1} 2920 and 1700; δ_H (400 MHz) 3.17 (1H, m), 3.10 (1H, m), 2.71 (1H, dd, *J* 19.1, 9.3), 2.46-2.35 (2H, m), 1.90-1.75 (2H, m) 1.58-1.40 (5H, m), 1.36-1.04 (4H, m), 0.89 (3H, s) and 0.87 (3H, s); δ_C (100 MHz) 210.5, 55.3, 53.3, 45.8, 41.6, 32.6, 30.2, 27.7, 25.1, 23.6, 22.3, 22.3 and 19.4; *m/z* 210 (M^+), 167, 139, 97, 81 and 67. (Found: M^+, 210.1665. $C_{13}H_{22}O_2$ requires M, 210.1619.)

1(1R, 2S*, 3R*)-1-[3-(1,2-epoxy-6,6-dimethylcyclohexanyl)]-2-propanone* **14a**.

Reaction of alkene **10** with *m*CPBA by the general procedure above, followed by flash chromatography (20% EtOAc – petrol) afforded the epoxide **14a** (64%) as a colourless oil; ν_{max} /cm^{-1} 2930, 1716, 1446, 1361, 1265, 1155 and 933; δ_H (270 MHz) 3.24-3.19 (2H, m), 2.71 (1H, dd, *J* 17.4, 10.3), 2.45 (1H, dd, *J* 17.3, 4.1), 2.21 (3H, s), 1.92-1.82 (2H, m), 1.22-1.22 (2H, m), 0.95 (1H, m), 0.90 (3H, s) and 0.77 (3H, s); δ_C (100 MHz) 208.8 (s), 54.5 (d), 54.1 (d), 41.4 (t), 37.4 (d), 30.7 (q), 29.5 (t), 28.3 (q), 26.3 (q) and 21.3 (t); *m/z* (CI) 183 (MH^+), 165 and 83. (Found: MH^+, 183.1385. $C_{11}H_{19}O_2$ requires M, 183.1385.)

1(1R, 2'S*, 3R*)-1-[3-(1,2-epoxycyclopentanyl)]-5-methyl-2-hexanone* **15a** and its *anti*-isomer **15b**.

Reaction of alkene **11** with *m*CPBA by the general procedure above afforded a 9:2 mixture of **15a** and **15b** according to ^{1}H NMR analysis of the crude product mixture. Flash chromatography (20% EtOAc – petrol) afforded the epoxides **15a** (78%) and **15b** (2%), as colourless oils. Less polar, **15a**, ν_{max} /cm^{-1} 2956, 1711, 1266, 853 and 736; δ_H (400 MHz) 3.43 (1H, m), 3.42 (1H, m), 2.68 (1H, dd, *J* 17.6, 7.8), 2.55 (1H, dd, *J* 17.6, 6.3), 2.45-2.16 (4H, m), 1.99 (1H, m), 1.72-1.44 (5H, m), 0.88 (3H, s) and 0.77 (3H, s); δ_C (100 MHz) 210.6 (s), 59.3 (d), 57.3 (d), 43.8 (t), 41.2 (t), 35.1 (d),

32.6 (t), 27.7 (d), 27.3 (t), 24.6 (t), 22.3 (q) and 22.3 (q); *m/z* 196 (M^+), 140 and 83. (Found: M^+, 196.1507. $C_{12}H_{20}O_2$ requires M, 196.1463.)

More polar, **15b**; δ_H (400 MHz) 3.45 (1H, d, *J* 2.4), 3.30 (1H, d, *J* 2.4), 2.69 (1H, m), 2.41 (2H, t, *J* 7.3), 2.35 (1H, d, *J* 15.6), 2.33 (1H, d, *J* 17.1), 1.96 (1H, m), 1.61-1.44 (5H, m), 1.20 (1H, m) and 0.89 (6H, d, *J* 6.4); δ_C (100 MHz) 208.0 (s), 59.8 (d), 56.6 (d), 43.8 (t), 41.1 (t), 34.3 (d), 32.6 (t), 27.7 (d), 25.2 (t), 24.5 (t) and 22.3 (q).

1(1R, 2S*, 3R*)-1-[3-(1,2-epoxycyclopentanyl)]-2-propanone* **16a.**

Reaction of alkene **12** with *m*CPBA by the general procedure above afforded a 5:1 mixture of **16a** and **16b** according to ^1H NMR analysis of the crude mixture (epoxide peaks for **16b** at 3.43 and 3.29 ppm). Flash chromatography (20% EtOAc – petrol) afforded the epoxide **16a** (83%) as a colourless oil, ν_{max} /cm^{-1} 2960, 1710 and 1350; δ_H (400 MHz) 3.44 (2H, s), 2.72 (1H, dd, *J* 18.0, 7.9), 2.86 (1H, dd, *J* 17.7, 6.1), 2.37 (1H, m), 2.16 (3H, s), 2.01 (1H, m), 1.74-1.55 (2H, m) and 0.94 (1H, m); δ_C (100 MHz) 208.0 (s), 59.3 (d), 57.3 (d), 44.8 (t), 35.1 (d), 30.3 (t), 27.3 (q) and 24.6 (t);*m/z* 140 (M^+), 122 (M^+-H_2O) and 83. (Found: M^+, 140.0847. $C_8H_{12}O_2$ requires M, 140.0837.)

b) *with MMPP: epoxidation of 1 and 12*

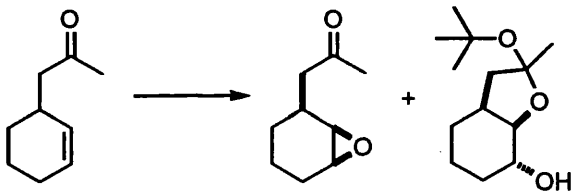
A stirred solution of alkene (0.3 mmol) in ethanol (3 cm^3) was treated portion wise with MMPP (0.3 mmol) under nitrogen and the mixture stirred overnight. The mixture was diluted with H_2O and extracted three times with CH_2Cl_2. The combined organics were washed successively with saturated aqueous sodium bicarbonate solution and water, dried ($MgSO_4$) and evaporated.

Epoxidation of **1** afforded exclusively **7a** (73%), identical by ^1H and ^{13}C NMR to the sample prepared using *m*CPBA.

Epoxidation of **12** produced a 7:1 ratio of **16a** : **16b** by ^{1}H NMR analysis of the crude mixture. Flash chromatography (20% EtOAc – petrol) provided **16a** (50%), identical by ^{1}H and ^{13}C NMR to the sample prepared using *m*CPBA.

c) *with $Mo(CO)_6$ / TBHP: epoxidation of **1** and **12***

tert-Butyl hydroperoxide (0.3 cm^3 of a 3M soln in isooctane, 0.9 mmol) and molybdenum hexacarbonyl (10 mg, 0.036 mmol, 0.1 equiv.) were added to a stirred solution of alkene (0.36 mmol) in benzene (3 cm^3). The mixture was heated at reflux until the reaction was complete (TLC). The mixture was then cooled and water was added. The organic layer was separated and the aqueous layer was extracted three times with ether. The combined organics were washed with saturated aqueous sodium sulfite solution, dried ($MgSO_4$) and evaporated to give the crude product.



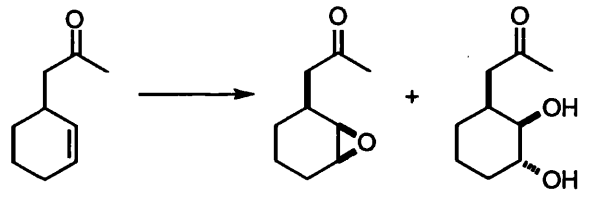
1 **7a** **17**

Epoxidation of alkene **1** by the above procedure resulted in a 3:2 mixture of epoxide **7a** and ketal **17** according to analysis of the crude ^{1}H NMR. Flash chromatography (20% EtOAc – petrol) afforded epoxide **7a** (30%), and ketal **17** (18%). Less polar **7a**, identical by ^{1}H NMR to the sample obtained by *m*CPBA epoxidation.

More polar **17**, ν_{max} /cm^{-1} 3420, 2978, 2934, 1456, 1362, 1190, 1119, 1007 and 870; δ_H (400 MHz) 3.94 (1H, t, *J* 6.4), 3.73 (1H, m), 2.61 (1H, m), 2.05 (1H, dd, *J* 13.4, 7.6), 1.81-1.58 (2H, m), 1.56 (1H, s), 1.53-1.25 (5H, m) and 1.24 (9H, s); δ_C (100 MHz) 110.7 (s), 83.7 (d), 79.5 (s), 70.7 (d), 40.7 (t), 36.3 (d), 29.5 (t), 26.6 (q), 26.3 (t), 24.6 (q) and 18.9 (t);*m/z* 155 (M^+-^{t}BuO), 137 (M^+-^{t}BuOH-H_2O), 73 (^{t}BuO) and 43 (CH_3CO). (Found: M^+-^{t}BuO, 155.1050. $C_9H_{15}O_2$ requires M-^{t}BuO, 155.1072.)

Epoxidation of alkene **12** by the above procedure resulted in a 3:2 mixture of epoxides **16a** : **16b** according to analysis of the crude ^{1}H NMR. Flash chromatography (20% EtOAc – petrol) afforded **16a** (25%) and **16b** (16%), identical by ^{1}H NMR to the samples obtained by *m*CPBA epoxidation.

*Epoxidation of **1** and **10** with dimethyldioxirane: Preparation of **7b**, **7c** and **14b**.*



1 **7a** **7c**

Dimethyldioxirane (0.5 cm^3 of a *ca.* 0.1M solution in acetone, 0.05 mmol) was added to a solution of the ketone **1** (6 mg, 0.04 mmol) in CH_2Cl_2 (1 cm^3). After 2 minutes the solvent was evaporated to give a film which was analysed by ^{1}H NMR and then subjected to flash chromatography (20% EtOAc – petrol) on deadened silica.

When the dimethyldioxirane solution had been dried with anhydrous potassium carbonate and stored over 4Å molecular sieves, the crude ^{1}H NMR showed a 1:1 mixture of *syn*-epoxide **7a** and diol **7c**. Flash chromatography yielded epoxide **7a** (3 mg, 50%) and diol **7c** (3 mg, 50%). Less polar, epoxide **7a**, identical by ^{1}H NMR to the sample prepared by *m*CPBA epoxidation of **1**.

More polar, diol **7c**, ν_{max} /cm^{-1} 3397 and 1703; δ_H (400 MHz) 3.59-3.52 (2H, m), 2.79 (1H, dd, *J* 16.8, 6.4), 2.63-2.57 (2H, m), 2.34 (1H, dd, *J* 17.1, 6.7), 2.18 (3H, s), 1.94 (1H, m) and 1.63-1.30 (4H, m); δ_C (100 MHz) 209.5, 75.3, 70.7, 42.6, 34.4, 31.6, 30.5, 28.5 and 19.5; *m/z* 172 (M^+), 154 (M-H_2O), 114 and 96. (Found: M^+, 172.1079. $C_9H_{16}O_3$ requires M, 172.1099.)

When the dimethyldioxirane solution had been dried only with anhydrous potassium carbonate, the crude ^{1}H NMR showed a 2.5:1 mixture of *syn*-epoxide **7a** and *anti*-epoxide **7b**. Flash chromatography yielded epoxides **7a** (30%) and **7b** (11%). Less

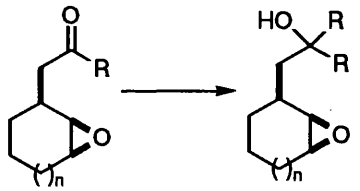
polar, epoxide **7a**, identical by ^{1}H NMR to the sample prepared by *m*CPBA epoxidation of **1**.

More polar, *anti*-epoxide **7b**, δ_H (400 MHz) 3.15 (1H, pentet, *J* 1.8), 2.84 (1H, d, *J* 3.7), 2.51 (2H, dd, *J* 15.0, 7.0), 2.37 (1H, m), 2.18 (3H, s), 2.05 (1H, dt, *J* 15.0, 4.3), 1.70-1.60 (2H, m), 1.39-1.24 (2H, m) and 0.77 (1H, m); δ_C (100 MHz) 207.5, 56.0, 52.6, 47.5, 30.4, 30.2, 26.7, 24.4 and 17.0; *m/z* 154 (M^+), 97, 70, 58 and 43. (Found: M^+, 154.1005. $C_9H_{14}O_2$ requires M, 154.0994.)

When ketone **10** was treated with dimethyldioxirane solution dried as above the ^{1}H NMR showed a 2:1 mixture of *syn*-epoxide **14a** and *anti*-epoxide **14b**. Flash chromatography yielded epoxides **14a** (22%) and **14b** (16%). Less polar, epoxide **14a**, identical by ^{1}H NMR to the sample prepared by *m*CPBA epoxidation of **10**.

More polar, *anti*-epoxide **14b**, ν_{max} /cm^{-1} 2928, 1720 and 1366; δ_H (400 MHz) 3.30 (1H, bm), 2.64 (1H, d, *J* 3.7), 2.57 (1H, dd, *J* 16.5, 3.0), 2.35 (1H, dd, *J* 16.5, 11.6), 2.22 (3H, s), 2.06 (1H, dd, *J* 11.8, 2.9), 1.99 (1H, m), 1.80 (1H, m), 1.39 (1H, td, *J* 13.1, 5.2), 1.07 (1H, m), 0.87 (3H, s) and 0.74 (3H, s); δ_C (100 MHz) 208.0, 54.8, 52.2, 43.4, 40.6, 32.6, 30.1, 29.9, 29.3, 21.2 and 20.8; *m/z* (CI) 183 (MH^+). (Found: MH^+, 183.1385. $C_{11}H_{19}O_2$ requires M, 183.1385.)

*Correlation experiments to prove syn-stereochemistry: General procedure for the reaction of keto-epoxides **7a**, **13a**, and **16a** with alkyl lithiums.*



The alkyl lithium reagent (1 equivalent in ether (methyllithium) or petrol (isoamyl lithium[111])) was added to a solution of the appropriate ketone (0.13 mmol) in THF (0.25 cm^3) at 0°C under nitrogen. After one hour the reaction was allowed to warm to room temperature. Saturated aqueous sodium bicarbonate solution was added to the reaction and the aqueous was extracted with CH_2Cl_2. The organics were separated, dried and the

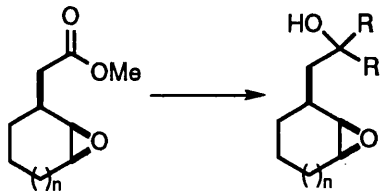
solvent evaporated. The residue was submitted to flash column chromatography on deadened silica to give the alcohols in fair yields.

Tertiary alcohol **6**, derived from **7a** and methyl lithium— Yield 45%. ν_{max} /cm^{-1} 3400; δ_H (270 MHz) 3.24 (1H, t *J* 3.3), 3.19 (1H, dt *J* 1.5, 3.7), 2.06 (1H, m), 1.92-1.70 (3H, m), 1.59-1.34 (3H, m), 1.25-1.12 (2H, m), 1.87-1.80 (3H, m), 1.51-1.36 (3H, m), 1.29 (3H, s) and 1.28 (3H, s); δ_C (67.5 MHz) 56.5, 54.0, 46.9, 30.6, 30.6, 29.4, 27.4, 23.7 and 19.6; *m/z* (CI) 171 (MH^+), 153 ($M-H_2O$) and 97.

Tertiary alcohol derived from **13a** and isoamyl lithium— Yield 45%. ν_{max} /cm^{-1} 3424, 2934 and 911; δ_H (400 MHz) 3.13-3.06 (2H, m), 1.92 (1H, m), 1.73-1.64 (2H, m), 1.50 (1H, s), 1.71-0.97 (15H, m), 0.78 (6H, d, *J* 6.4), 0.77 (6H, d, *J* 6.9); δ_C (100 MHz) 74.8 (s), 56.8 (d), 54.0 (d), 43.0 (t), 42.9 (t), 37.8 (t), 36.6 (t), 32.8 (t), 32.5 (t), 30.4 (d), 28.6 (d), 27.5 (t), 23.8 (t), 22.7 (q) and 19.9 (t); *m/z* (FAB) 283 (MH^+), 265 (M-OH), 211 and 81.

Tertiary alcohol derived from **16a** and methyl lithium— Yield 33%; ν_{max} /cm^{-1} 3430; δ_H (400 MHz) 3.50 (1H, s), 3.44 (1H, s), 2.16 (1H, m), 2.01 (1H, dd, *J* 13.2, 7.8), 1.82 (1H, dd, *J* 14.2, 7.3), 1.73-1.55 (4H, m), 1.29 (3H, s), 1.27 (3H, s) and 0.98 (1H, m); δ_C (100 MHz) 71.0 (s), 60.6 (d), 57.4 (d), 44.7 (t), 36.0 (d), 30.6 (q), 29.4 (q), 27.4 (t) and 26.5 (t); *m/z* (CI) 157 (MH^+), 139 (M-OH), 121, 83 and 73.

Preparation of the tertiary alcohols from the appropriate epoxy methyl ester and alkyl lithium.



The ester **5** was prepared as described by Kocovsky.[50b] The corresponding 5-membered ring methyl ester was prepared in the same way.

Methyl (1S, 2R*, 3S*)-2-[3-(1,2-epoxycyclopentanyl)]-acetate* **46a**.—Yield 67%; (Found C, 61.1; H, 8.0. $C_8H_{12}O_3$ requires C, 61.5; H, 7.8%); ν_{max} /cm^{-1} 3024, 2951, 1737, 1439 and 1198; δ_H (400 MHz) 3.67 (3H, s), 3.44 (2H, s), 2.55 (1H, dd, *J* 16.2, 7.9), 2.44-2.31 (2H, m), 2.01 (1H, m), 1.71-1.58 (2H, m) and 0.97 (1H, m); δ_C (75 MHz) 173.2 (s), 59.0 (d), 57.3 (d), 51.5 (q), 36.4 (d), 35.2 (t), 27.2 (t) and 24.6 (t); *m/z* (CI) 157 (MH^+), 139, 125, 97, 83 and 67.

The alkyl lithium (1 equivalent) was added to a solution of the appropriate ester (0.13 mmol) in THF (0.25 cm^3) under a nitrogen atmosphere at -78 °C. After one hour the reaction was allowed to warm to room temperature. Saturated aqueous sodium bicarbonate solution was added to the reaction and the aqueous was extracted with CH_2Cl_2. The organics were separated, dried and the solvent evaporated. The reaction gave good yields of tertiary alcohol, identical in all cases by ^1H and ^{13}C NMR to those prepared by addition of alkyl lithiums to the ketones.

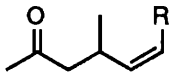
Keto-alkene ***1a****, ^{18}O labelled.*

Trimethyl orthoformate (1 cm^3, 1 mmol) was added to a solution of the ketone **1** (10 mg, 0.07 mmol) in methanol (1 cm^3) with several crystals of *p*-toluenesulfonic acid and flame dried 4Å molecular sieves under nitrogen. The reaction was heated to reflux for 150 minutes. The mixture was then diluted with saturated aqueous sodium bicarbonate

solution and extracted three times with CH_2Cl_2. The combined organics were dried ($MgSO_4$) and the solvents evaporated to give the crude ketal **8** (13 mg, 98%), as an oil , δ_H (270 MHz) 5.69 (2H, s), 3.20 (6H, s), 2.40-0.80 (9H, m) and 1.30 (3H, s).

^{18}O labelled water (Aldrich, 95 atom% ^{18}O; 147 cm^3, 7 mmol) and 98% sulfuric acid (1 drop from a small capillary tube) were added to a solution of the crude dimethylketal **8** (143 mg, 0.7 mmol) in THF (2.5 cm^3) under nitrogen. After 1 hr triethylamine (1 cm^3, 7 mmol) was added and the mixture stirred for a further 5 minutes before being subjected to flash chromatography on deadened silica (10% EtOAc – petrol), to yield ^{18}O labelled ketone (83 mg, 76%). Evidence for label incorporation was provided by mass spectrometry (*m/z* = 140) and ^{13}C NMR analysis of a *ca.* 1:1 mixture of this labelled product with unlabelled ketone (two carbonyl resonances observed, at 208.399 and 208.344 ppm). Ketone **68** was prepared in an identical manner to keto-alkene **1a**. Evidence for label incorporation was provided by mass spectrometry (*m/z* = 156) and ^{13}C NMR analysis of a *ca.* 1:1 mixture of this labelled product that resulted from the reaction (212.60 and 212.56 ppm). ^{18}O labelled cyclohexanone was also prepared in a manner identical to that described above. The work up procedure differed only in that after quenching the reaction with triethylamine, the solution was filtered *via* celite, dried (Na_2SO_4) and the solvent evaporated to yield an oil (84%). Evidence for label incorporation was provided by mass spectrometry (*m/z* = 100) which indicated that label incorporation was > 80%.

*Synthesis of acyclic keto-alkenes **18** and **71***



18, R = Pr
71, R = Bu

Butyl lithium (26.5 cm^3 of a 2.5M solution in hexanes, 66.25 mmol) was added to the appropriate terminal alkyne (62 mmol) in ether (22 cm^3) at -78°C under nitrogen. The mixture was stirred for 15 mins and then added to a suspension of CuI (12.5 g, 66

mmol) in ether (160 cm^3), also under nitrogen at -78°C. After 40 mins iodotrimethylsilane (11 cm^3, 77 mmol) was added to the deep brown mixture and after a further 5 mins pent-3-en-2-one (3.5 cm^3, 35.6 mmol) in ether (20 cm^3) was also introduced into the reaction. The mixture was stirred at -78°C for a further 6 hrs then allowed to warm to room temperature whilst stirring overnight. Pyridine (16 cm^3) was added to complex out the copper salts followed after 3 hrs by 2M HCl (165 cm^3). The resulting suspension was filtered over celite, the organics were separated and the aqueous extracted twice with ether. The combined organics were washed successively with 2M HCl, saturated aqueous sodium bicarbonate solution and brine, dried ($MgSO_4$), and the solvent evaporated. Flash chromatography of the residue (17% EtOAc – petrol) afforded the alkynes and as very volatile oils.

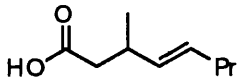
Z-4-Methyl-non-5-yne-2-one **20**.—Yield: 10%; δ_H (270 MHz) 2.90 (1H, t sextet, *J* 7.0, 2.2), 2.61 (1H, dd, *J* 16.1, 7.3), 2.44 (1H, dd, *J* 16.1, 7.0), 2.15 (3H, s), 2.08 (2H, dt, *J* 7.1, 2.2), 1.46 (2H, sextet, *J* 7.3), 1.14 (3H, d, *J* 7.0) and 0.93 (3H, t, *J* 7.3); δ_C (67.5 MHz) 207.0, 83.4, 80.7, 50.9, 30.4, 22.4, 21.9, 21.3, 20.6 and 13.3.

A solution of the appropriate keto-alkyne **20** or **70** (4.40 mmol) in dry hexane (100 cm^3) containing quinoline (24 μl) was charged with Lindlar catalyst (134 mg) and hydrogenated at 1 atm for 20 min. The reaction was then filtered on a celite / sodium sulfate pad, washing through with ether (400 cm^3). The filtrate was evaporated under reduced pressure to give a yellow liquid which was pre-adsorbed onto silica gel (Merck 9385) prior to purification by flash chromatography (10% ether – petrol) to afford the keto-alkenes **18** and **71** as a pale yellow, sweet-smelling liquid.

Z-4-Methyl-non-5-en-2-one **18**.—Yield 100%; ν_{max} /cm^{-1} 2959, 1716, 1456, 1359, 1167 and 734; δ_H (400 MHz) 5.31 (1H, dt, *J* 10.7, *J* 7.3), 5.15 (1H, bt, *J* 10.0), 3.01 (1H, m), 2.37 (2H, d, *J* 7.0), 2.11 (3H, s), 2.08-1.98 (2H, m), 1.42-1.30 (2H, m), 0.97 (3H, d, *J* 6.7) and 0.90 (3H, t, *J* 7.3); δ_C (100 MHz) 208.3 (s), 134.2 (d), 129.2 (d), 51.1 (t), 30.5 (q), 29.4 (t), 28.2 (d), 22.8 (t), 21.1 (q) and 13.7 (q); *m/z* 154 (M^+), 139 (M^+-CH_3), 111, 69 and 43. (Found: M^+, 154.1374. $C_{10}H_{18}O$ requires M, 154.1358.)

Z-4-Methyl-dec-5-en-2-one **71**.—Yield 57%; ν_{max} /cm^{-1} 2958, 2928, 1716, 1462, 1358 and 1165; δ_H (400 MHz) 5.30 (1H, dt, *J* 10.7, 7.3), 5.13 (1H, m), 2.97 (1H, m), 2.36 (2H, d, *J* 7.0), 2.11 (3H, s), 2.09-2.02 (2H, m), 1.35-1.27 (4H, m), 0.96 (3H, d, *J* 6.7) and 0.89 (3H, t, *J* 3.5); δ_C (100 MHz) 208.4 (s), 134.0 (d), 129.5 (d), 51.2 (t), 31.9 (t), 30.6 (q), 28.2 (d), 27.1 (t), 22.4 (t), 22.1 (q) and 14.0 (q); *m/z* (CI) 169 (MH^+), 110 and 44. (Found: MH^+, 169.1592. $C_{11}H_{21}O$ requires MH, 169.1592.)

E-3-Methyl-oct-4-enoic acid **23**.

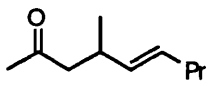


23

Propyl magnesium chloride (50 cm^3 of a 2M solution in ether, 100 mmol) was added to a stirred solution of crotonaldehyde (8 cm^3, 100 mmol) in ether (50 cm^3) under nitrogen at 0°C. After the addition the reaction was allowed to warm to room temp. When completed the reaction was diluted with 2M HCl (30 cm^3) and water (50 cm^3). The organics were separated and the aqueous extracted three times with ether. The combined organics were washed with saturated aqueous sodium bicarbonate solution then brine, dried ($MgSO_4$) and the solvent evaporated to yield crude hept-2-en-4-ol **21** (8.98 g, 78%). A solution of this crude hept-2-en-4-ol **21** (8.98 g, 79 mmol) and propionic acid (1 cm^3) in triethylorthoacetate (200 cm^3) was heated at 140°C for 8 hrs. The reaction was allowed to cool to room temperature and was then diluted with ethyl acetate and washed twice with 2M HCl, saturated aqueous sodium bicarbonate solution and brine. The organic layer was dried and the solvent evaporated to yield crude *E*-ethyl 3-methyl-oct-4-enoate **22** (14.55 g, 100%). Sodium hydroxide (80 cm^3 of a 1M aqueous solution) was added to this crude ethyl ester (14.55 g, 79 mmol) in methanol (80 cm^3) and the mixture stirred rapidly for 24 hrs. The reaction was then diluted with CH_2Cl_2 and water , the organic layer separated and the aqueous extracted twice with CH_2Cl_2. The combined organics were discarded. The aqueous was acidified (2M HCl) and extracted three times with CH_2Cl_2. The combined organics were dried ($MgSO_4$) and the solvent evaporated to

yield E-*3-methyl-oct-4-enoic acid* **23** (9.29 g, 75%), ν_{max} /cm^{-1} 2929, 1710, 1410, 1294 and 969; δ_H (270 MHz) 5.48-5.30 (2H, m), 2.63 (1H, sept, *J* 7.0), 2.4 (2H, dd, *J* 6.3, 0.9), 1.97 (2H, q, *J* 7.0), 1.36 (2H, hex, *J* 7.3), 1.06 (3H, d, *J* 6.8) and 0.88 (3H, t, *J* 7.3); δ_C (67.5 MHz) 179.1 (s), 133.9 (d), 129.7 (d), 41.8 (t), 34.5 (t), 33.4 (d), 22.5 (t), 20.4 (q) and 13.5 (q); *m/z* 156 (M^+), 138 (M^+-H_2O), 127 (M^+-CO), 113 (M^+-CO_2) and 81. (Found: M^+, 156.1159. $C_9H_{16}O_2$ requires M, 156.1150.)

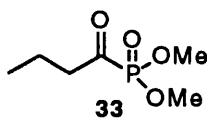
E-*4-Methyl-non-5-en-2-one* **19**.



19

Following the general procedure described earlier (for the preparation of **1**, **9**, **10**, **11** and **12**), *E*-3-Methyl-oct-4-enoic acid **23** reacted with methyl lithium to afford the ketone **19** (40%), ν_{max} /cm^{-1} 2959, 1716, 1456, 1362 and 969; δ_H (400 MHz) 5.40 (1H, dt, *J* 15.3, 6.4), 5.30 (1H, dd, *J* 15.5, 6.9), 2.65 (1H, septet, *J* 7.0), 2.43 (1H, dd, *J* 15.6, 7.0), 2.34 (1H, dd, *J* 15.6, 7.0), 2.11 (3H, s), 1.93 (2H, q, *J* 7.3), 1.34 (2H, sextet, *J* 7.3), 0.99 (3H, d, *J* 6.7) and 0.86 (3H, t, *J* 7.3); δ_C (100 MHz) 208.5 (s), 134.4 (d), 129.1 (d), 51.1 (t), 34.5 (t), 32.8 (d), 22.5 (t), 20.1 (q) and 13.5 (q); *m/z* 154 (M^+), 139 (M^+-CH_3), 111, 97, 81, 69 and 43. (Found: M^+, 154.1353. $C_{10}H_{18}O$ requires M, 154.1368.)

Dimethyl Butyrylphosphonate **33**.



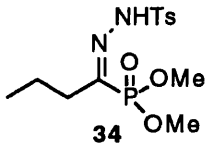
33

Trimethyl phosphite (12 cm^3, 100 mmol) was added over *ca.* 20 minutes into a solution of butyrylchloride (10 cm^3, 96 mmol) in ether, at 0°C in a flask fitted with a

reflux condenser. The reaction was stirred overnight and the solvents were distilled away *in vacuo* to yield **33** as a viscous oil (10.3 g, 100%).

ν_{max} /cm^{-1} 3490, 2962, 1693, 1462, 1260, 1031 and 835; δ_H (400 MHz) 3.8 (6H, dd, *J* 10.5, 1.1), 2.75 (2H, dt, *J* 7.1, 1.1), 1.61 (2H, hex, *J* 7.3) and 0.88 (3H, dt, *J* 7.3, 0.8); δ_C (100 MHz) 209.6, 53.7, 45.6, 45.1, 15.8 and 13.3; *m/z* 180 (M^+), 137, 110, 109, 71 and 43. (Found: M^+, 180.0569. $C_6H_{13}O_4P$ requires M, 180.0552.)

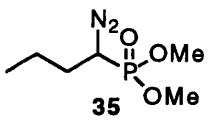
Dimethyl-1-oxobutanphosphonate p-toluenesulfonyl hydrazone ***34****.*



34

A solution of *para*-toluenesulfonylhydrazine (9.32 g, 50 mmol) and keto-phosphonate **33** (10 g, 50 mmol) in methanol (250 cm^3) was left to stand at room temperature for 24 hrs. The solvent was evaporated and the residue recrystalised from methanol to yield **34** (14.79 g, 76%). (Found C, 44.8; H, 6.19; N, 8.12. $C_{13}H_{20}N_2O_3$ requires C, 44.8; H, 6.1; N, 8.0%); ν_{max} /cm^{-1} 3019, 1348, 1216 and 753. δ_H (400 MHz) 8.42 (1H, s), 7.79 (2H, d, *J* 8.2), 7.32 (2H, d, *J* 8.2), 3.71 (6H, d, *J* 10.7), 2.43 (3H, s), 2.34-2.27 (2H, m), 1.57-1.51 (2H, m) and 0.92 (3H, t, *J* 7.3); *m/z* (CI) 349 (MH^+), 257, 193, 165 and 109.

α-Diazobutyldimethylphosphonate **35.**

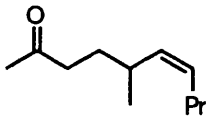


35

Potassium carbonate (438 mg, 3.5 mmol) was added to a stirred biphasic solution of **34** (1.02 g, 2.9 mmol) in 1:1 ether / water (12 cm^3). Every few hours the ethereal layer was changed, the old layer being decanted into a conical flask. After 48 hrs the aqueous layer was extracted twice with ether, these ethereal extractions were combined with the

previous ethereal layers, dried ($MgSO_4$) and the solvent evaporated. The residue was purified by flash column chromatography on neutral alumina (20% ether – petrol) to yield **35** (261 mg, 46%); ν_{max} /cm^{-1} 3487, 2959, 2874, 2078, 1462, 1260, 1183, 1019 and 827; δ_H (270 MHz) 3.70 (6H, d, *J* 11.7), 2.06 (2H, dt, *J* 10.4, 7.3), 1.49 (2H, sextet, *J* 7.5), 0.93 (3H, t, *J* 7.3); δ_C (100 MHz) 52.7, 52.6, 25.7, 25.6, 21.4 and 13.1.

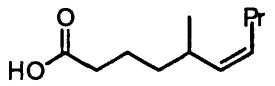
Z- 5-methyl-dec-6-en-2-one **28.**



28

Sodium hexamethyldisilazide (39 cm^3 of a 1M solution in THF, 39 mmol) was added to a stirred suspension of n-butyl triphenylphosphonium bromide (15.56 g, 39 mmol) in toluene (250 cm^3), under nitrogen. The deep red mixture was cooled to -78°C and a solution of aldehyde **32**[78] (5g, 39 mmol) in toluene (150 cm^3) was added. After 30 minutes the reaction was warmed to room temperature and stirred for another 30 minutes before being quenched with water. The organic layer was separated and the aqueous was extracted with ether. The combined organics were washed with water, dried ($MgSO_4$) and the solvent evaporated. Flash chromatography of the residue (5% EtOAc – petrol) afforded **28** (5.1 g, 85%); ν_{max} /cm^{-1} 2958, 1718, 1457 and 1165; δ_H (400 MHz) 5.33 (1H, dt, *J* 11.0, 7.3), 5.06 (1H, tt, *J* 10.5, 1.5), 2.43-2.36 (3H, m), 2.11 (3H, s), 2.00-1.93 (2H, m), 1.63 (1H, m), 1.44-1.32 (3H, m), 0.94 (3H, d, *J* 6.4) and 0.89 (3H, t, *J* 7.3); δ_C (100 MHz) 209.3 (s), 135.3 (d), 129.3 (d), 41.8 (d), 31.7 (t), 31.1 (q), 29.9 (t), 29.5 (t), 22.9 (t), 21.4 (q) and 13.8 (q); *m/z* 168 (M^+), 150 (M^+-H_2O), 125, 110, 95, 81 and 43. (Found: M^+, 168.1475. $C_{11}H_{20}O$ requires M, 168.1514.)

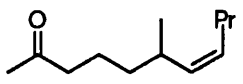
Z-5-methyl-dec-6-enoic acid **39**.



39

Sodium hexamethyldisilazide (15.5 cm^3 of 1M soln in THF, 15.5 mmol) was added to a stirred suspension of n-butyl triphenylphosphonium bromide (6.2 g, 15.5 mmol) in toluene (90 cm^3), under nitrogen. The deep red reaction mixture was cooled to -78°C, and a solution of aldehyde **38**[81] (1.1 g, 7.75 mmol) in toluene (60 cm^3) was added. After 30 minutes the reaction was warmed to room temperature and stirred for another 30 minutes before being quenched with water. The organic layer was separated and the aqueous extracted with ether. The combined organics were discarded. The aqueous layer was acidified with 2M HCl and extracted three times with ether. The combined organics were dried ($MgSO_4$) and the solvent evaporated. Flash chromatography of the residue (40% EtOAc – petrol +1% AcOH) afforded acid **39** (1.12 g, 80%), ν_{max} /cm^{-1} 3427, 1709, 1411 and 909; δ_H (400 MHz) 5.32 (1H, dt, *J* 11.0, 7.3), 5.10 (1H, tt, *J* 11.0, 1.5), 2.43 (1H, m), 2.32 (2H, t, *J* 7.5), 2.02-1.96 (2H, m), 1.65-1.52 (2H, m), 1.41-0.95 (4H, m), 0.93 (3H, d, *J* 6.4) and 0.89 (3H, t, *J* 7.3); δ_C (100 MHz) 180.3 (s), 135.7 (d), 128.8 (d), 36.8 (t), 34.2 (t), 31.4 (d), 29.5 (t), 22.9 (t), 22.7 (t), 21.3 (q) and 13.8 (q); *m/z* 184 (M^+), 141, 128, 110, 97 and 81. (Found: M^+, 184.1461. $C_{11}H_{20}O_2$ requires M, 184.1463.)

Z-6-Methyl-undec-7-en-2-one **30**.

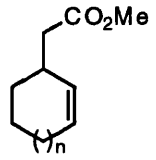


30

Following the general procedure described earlier (for the preparation of **1**, **9**, **10**, **11** and **12**), reaction of acid **39** with methyl lithium afforded ketone **30** (61%.), ν_{max} /cm^{-1} 2957, 1719, 1460, 1358, 1164; δ_H (400 MHz) 5.27 (1H, dtt, *J* 10.9, 7.3, 0.6),

5.07 (1H, tt, *J* 11.0, 1.5), 2.43-2.38 (1H, m), 2.35 (2H, t, *J* 7.0), 2.08 (3H, s), 1.99-1.92 (2H, m), 1.55-1.44 (2H, m), 1.37-1.21 (2H, m), 1.16-1.07 (2H, m), 0.89 (3H, d, *J* 6.4) and 0.86 (3H, t, *J* 7.3); δ_C (100 MHz) 209.1 (s), 135.8 (d), 128.6 (d), 43.8 (t), 36.9 (t), 31.4 (d), 29.7 (q), 29.5 (t), 22.9 (t), 21.8 (t), 21.2 (q) and 13.7 (q); *m/z* 182 (M^+), 164 (M^+-H_2O), 124, 95, 81 and 43. (Found: M^+, 182.1703. $C_{12}H_{22}O$ requires M, 182.1671.)

Esterification of acid 3 and 2-cyclopenten-1-acetic acid: Preparation of esters 44 and 45[50b]

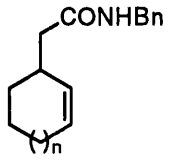


44, n = 0
45, n = 1

Oxalyl chloride (0.2 cm^3, 2.4 mmol) was added to a solution of the appropriate acid (1.95 mmol) in CH_2Cl_2 (2 cm^3) under nitrogen and stirred for *ca.* 30 minutes. After this time methanol (3 cm^3) was added and the reaction stirred for a further 10 minutes before the solvent was evaporated. Flash column chromatography (10% EtOAc – petrol) gave good yields of the esters.

Methyl 2-[cyclopent-2-enyl] acetate **44**.—Yield 77%; ν_{max} /cm^{-1} 2949, 2853, 1739, 1437, 1358, 1259, 1170 and 1005; δ_H (400 MHz) 5.76 (1H, ddd, *J* 7.9, 3.4, 2.1), 5.66 (1H, ddd, *J* 7.6, 4.3, 2.1), 3.68 (3H, s), 3.07 (1H, m), 2.41-2.27 (4H, m), 2.17-2.09 (1H, m) and 1.45 (1H, m); δ_C (100 MHz) 173.4 (s), 133.6 (d), 131.5 (d), 51.4 (q), 41.9 (d), 40.2 (t), 31.8 (t) and 29.6 (t); *m/z* 140 (M^+), 125, 109, 97, 81, 67, 55, 53 and 39. (Found: M^+, 140.0837. $C_8H_{12}O_2$ requires M, 140.0750.)

*Synthesis of amides **48**, **49**[50b] from the corresponding acids and benzylamine*

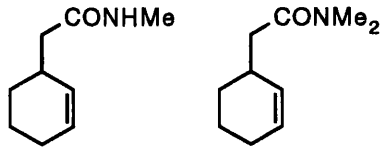


48, n = 0
49, n = 1

Amide **49** was prepared according to the procedure of Kocovsky.[50b] Previously unreported amide **48** was prepared in the same way. 1-Hydroxybenzotriazole (225 mg, 1.57 mmol) was added to a solution of appropriate acid (1.43 mmol) and benzylamine (170 μl, 1.56 mmol) in DMF (4 cm^3) and the mixture stirred at room temperature for 5 minutes. After this time DCC (325 mg, 1.58 mmol) in DMF (2 cm^3) was added and the mixture stirred for a further 12 hrs. Precipitated DCU was filtered, and the filtrate was concentrated on a rotary evaporator. The residue was partitioned between saturated aqueous $(NH_4)_2SO_4$ and ether. The ethereal layer was washed successively with 5% HCl, brine, 5% aqueous $KHCO_3$, dried with $MgSO_4$ and the solvent evaporated. The residue was dissolved in 80% benzene - chloroform and filtered through a pad of aluminium oxide. The filtrate was concentrated to yield pure N-benzylamides **48** and **49**.

N-benzyl 2-[cyclopent-2-enyl] acetamide **48**.—Yield 100%. ν_{max} /cm^{-1} 3743, 3284, 2927, 1643, 1555 and 1454; δ_H(400 MHz) 7.29-7.19 (5H, m), 5.69 (1H, ddd, *J* 7.6, 4.3, 2.1), 5.67-5.64 (1H, m), 5.61 (1H, ddd, *J* 7.6, 3.9, 2.1), 4.38 (2H, d, *J* 5.8), 3.08 (1H, m), 3.05-2.03 (4H, m) and 1.39 (1H, m); δ_C (100 MHz) 171.9 (s), 138.4 (d), 133.9 (d), 131.6 (d), 128.7 (d), 127.8 (d), 127.5 (d), 43.6 (t), 42.9 (t), 42.6 (d), 31.9 (t) and 29.6 (t); *m/z* (CI) 216 (MH^+), 215 (M^+), 149, 91 and 67. (Found: M^+, 215.1311. $C_{14}H_{17}NO$ requires M, 215.1310.)

*Synthesis of amides **50** and **51** from acid **3** and the appropriate amine*



50 **51**

Oxalyl chloride (0.15 cm^3, 1.8 mmol) was added to a solution of acid **3** (200 mg, 1.43 mmol) in CH_2Cl_2 (4 cm^3) under nitrogen. After 1 hr a 1:1 solution of aqueous amine (2.86 mmol) and NaOH (2.86 cm^3 of 1M solution) in water (4 cm^3) was added to the acid chloride. The reaction was stirred for 48 hrs, after which time the solution was diluted with CH_2Cl_2 and water. The organic layer was separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organics were washed with 2M HCl, water and dried ($MgSO_4$). The solvent was evaporated and the crude amide was purified by flash column chromatography (50% EtOAc – petrol) to yield amides **50** and **51**.

N-methyl 2-[cyclohex-2-enyl] acetamide **50**.—Yield 68%; (Found C, 70.1; H, 10.2; N, 9.0. $C_9H_{15}NO$ requires C, 70.5; H, 9.9; N, 9.2%); ν_{max} /cm^{-1} 3294, 2927, 1648 and 1558; δ_H (270 MHz) 5.71 (1H, m), 5.56 (1H, m), 5.55 (1H, bm), 2.82 (3H, d, *J* 4.9), 2.63 (1H, m), 2.22-2.05 (2H, m), 1.98 (1H, m), 1.85-1.51 (4H, m) and 1.13-1.21 (1H, m); δ_C (100 MHz) 172.6 (s), 130.4 (d), 128.1 (d), 43.3 (t), 32.6 (d), 28.8 (t), 26.2 (q), 25.0 (t) and 20.9 (t); *m/z* (CI) 154 (MH^+), 137, 73 and 58.

N, N- dimethyl 2-[cyclohex-2-enyl] acetamide **51**.—Yield 32%; ν_{max} /cm^{-1} 3482, 2925, 1645, 1496, 1456, 1397, 1268 and 1146; δ_H (270 MHz) 5.68 (1H, m), 5.56 (1H, dd, *J* 10.0, 1.8), 2.99 (3H, s), 2.94 (3H, s), 2.64 (1H, m), 2.15 (2H, d, *J* 0.7), 2.00-1.96 (2H, m), 1.84 (1H, m), 1.79-1.50 (2H, m) and 1.24 (1H, m); δ_C (100 MHz) 172.1 (s), 131.0 (d), 127.7 (d), 39.4 (t), 37.4 (q), 35.4 (q), 32.2 (d), 29.1 (t), 25.1 (t) and 21.1 (t); *m/z* 167 (M^+), 152, 95, 81, 72, 56 and 42. (Found: M^+, 167.1310. $C_{10}H_{17}NO$ requires M, 167.1310.)

Epoxidation of esters ***44*** *and* ***45***[50b] *and amides* ***48***, ***59***,[50b] ***50*** *and* ***51*** *with dimethyldioxirane: Preparation of* ***46a***, ***47a***,[50b] ***52a***, ***53a***,[50b] ***54a*** *and* ***55a***.

Dimethyldioxirane (0.5 cm^3 of a *ca.* 0.1M solution in acetone, 0.05 mmol) was added to the neat ester or amide (0.04 mmol) and stirred. When the reaction was shown to be complete by TLC, the solvent was evaporated to yield the appropriate products which were analysed by ^1H NMR and then purified by flash chromatography on neutralised silica.

(1S, 2R*, 3S*)-N-Benzyl-2-[3-(1,2-epoxycyclopentanyl)]-acetamide* **52a**.—Yield 84%; (Found C, 72.7; H, 7.7; N, 6.2%. $C_{14}H_{17}NO_2$ requires C, 72.7; H, 7.4; N, 6.1%); ν_{max} /cm^{-1} 3292, 2930, 1646, 1548, 1453, 1215 and 1024; δ_H (270 MHz) 7.29-7.19 (5H, m), 6.00-5.80 (1H, m), 4.37 (2H, q, *J* 2.9), 3.37 (2H, dd, *J* 6.0, 2.6), 2.54-2.29 (3H, m), 2.05 (1H, m), 1.78-1.57 (2H, m) and 0.98 (1H, m); δ_C (100 MHz) 171.1 (s), 138.2 (s), 128.7 (d), 127.7 (d), 127.5 (d), 59.3 (d), 57.5 (d), 43.6 (t), 37.9 (t), 36.9 (d), 24.7 (t) and 24.6 (t); *m/z* (+FAB) 232 (MH^+), 214, 165, 123, 109 and 106.

(1S, 2R*, 3S*)-N-Methyl-2-[3-(1,2-epoxycyclohexanyl)]-acetamide* **54a**.—Yield 73%; (Found C, 63.6; H, 9.0; N, 8.1%. $C_9H_{15}NO_2$ requires C, 63.9; H, 8.9; N, 8.3%); ν_{max} /cm^{-1} 3853, 3308, 2932, 1649 and 1558; δ_H (400 MHz) 5.50 (1H, m), 3.19 (1H, t, *J* 4.0), 3.09 (1H, m), 2.78 (3H, d, *J* 4.1), 2.46-2.33 (2H, m), 2.16 (1H, m), 1.88-1.73 (2H, m), 1.46-1.35 (2H, m) and 1.25-1.05 (2H, m); δ_C (100 MHz) 172.3, 55.1, 53.6, 40.2, 32.0, 26.3, 25.1, 23.6 and 19.3; *m/z* 170 (MH^+ self protonated), 152 and 98.

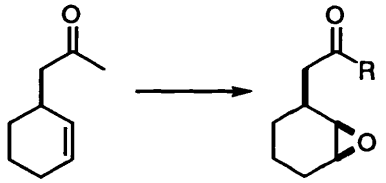
(1S, 2R*, 3S*)-N, N-Dimethyl-2-[3-(1,2-epoxycyclohexanyl)]-acetamide* **55a**.—Yield 73%; ν_{max} /cm^{-1} 2933, 1643, 1497, 1398, 1262, 1122 and 1060; δ_H (400 MHz) 3.21-3.17 (2H, m), 3.03 (3H, s), 2.95 (3H, s), 2.56 (1H, dd, *J* 15.1, 7.8), 2.48 (1H, m), 2.28 (1H, dd, *J* 15.1, 5.6), 1.88-1.75 (2H, m), 1.49-1.40 (2H, m), 1.27-1.22 (1H, m) and 1.14-1.09 (1H, m). δ_C (100 MHz) 171.7, 55.6, 53.5, 37.3, 36.4, 35.4, 31.8, 25.3,

23.6 and 19.7; *m/z* 183 (M^+), 166, 138, 112 and 87. (Found: M^+, 183.1260. $C_{10}H_{17}NO_2$ requires M, 183.1259.)

*Correlation experiments to prove syn-stereochemistry: General procedure for the reaction of amides **48**, **59**, **50** and **51** with mCPBA.*

Amides **48**, **59**[50b], **50** and **51** were treated with *m*CPBA according to the procedure of Kocovsky,[50] which has been shown to generate the *syn* epoxy-amide isomer predominantly. The major isomers from this reaction were spectroscopically identical to the major isomers produced from the reaction of the appropriate amide with DMDO.

Epoxidation of the Keto-alkenes using the Biphasic Buffered Oxone® System



1 **7a**

a) *The pre-mixing modification to Curci's procedure.*

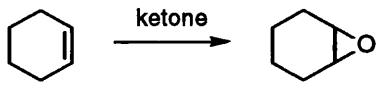
This procedure was used for all the intramolecular epoxidation reactions on keto-alkene **1** in Table 26. A solution of Oxone® (4.52 g, 14.9 mmol of $KHSO_5$) and $(EDTA)Na_2$ (12.5 mg) in distilled water (31.25 cm^3) was premixed with 0.5M KOH solution until the pH=7.5. This solution was added dropwise over *ca.* 35 minutes to a stirred biphase of keto-alkene **1** (50 mg, 0.36 mmol) and Bu_4NHSO_4 (107 mg, 0.3 mmol) in CH_2Cl_2 (2.5 cm^3) and pH 7.5 phosphate buffer solution (5 cm^3) at 0°C. The pH was adjusted to 7.5 and kept at this value by dropwise addition of 0.5M KOH when needed. After 24 hrs the organic layer was separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organics were washed once in succession with saturated aqueous sodium sulfite solution, saturated aqueous sodium bicarbonate

solution, and brine. The dried ($MgSO_4$) organic layer was evaporated and the residue was purified by flash chromatography (20% EtOAc – petrol) on deadened silica to yield keto-epoxide **7a** (30 mg, 55%), which was identical in every respect to the product of the reaction of keto-alkene **1** with *m*CPBA.

b) *The $NaHCO_3$ buffering procedure.*

This procedure was used for all the intramolecular epoxidation reactions on the keto-alkenes except for those detailed in Table 26. A solution of Oxone® (4.52 g, 14.9 mmol of $KHSO_5$) and $(EDTA)Na_2$ (12.5 mg) in distilled water (31.25 cm^3) was added to a stirred biphase of keto-alkene **1** (50 mg, 0.36 mmol) and Bu_4NHSO_4 (107 mg, 0.3 mmol) in CH_2Cl_2 (2.5 cm^3) and 1M sodium bicarbonate solution (22 cm^3) at 0°C. The pH after the addition of the Oxone® solution was 7.24. After 24 hrs the pH had risen to 8.72, the organic layer was separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organics were washed once successively with saturated aqueous Na_2SO_3 solution, saturated aqueous sodium bicarbonate solution, and brine. The dried ($MgSO_4$) organic layer was evaporated and the residue was purified by flash chromatography (20% EtOAc – petrol) on deadened silica to yield keto-epoxide **7a** (30 mg, 55%), which was identical in every respect to the product of the reaction of keto-alkene **1** with *m*CPBA.

Epoxidation of cyclohexene using the Biphasic Buffered Oxone® System



This procedure was used for the intermolecular epoxidation of cyclohexene in all cases. When a ketone[112] was used as a promoter it was either acetone, ^{18}O labelled 4-*tert*butylcyclohexanone, ^{18}O labelled cyclohexanone, 2-butanone or 2-hexanone. A solution of Oxone® (3.68 g, 12 mmol of $KHSO_5$) and $(EDTA)Na_2$ (20 mg) in distilled

water (30 cm^3) was added to a stirred biphase of cyclohexene (0.52 cm^3, 5 mmol), Bu_4NHSO_4 (400 mg, 1 mmol) and ketone (5 or 25 mmol)[111] in CH_2Cl_2 (50 cm^3) and 1M sodium bicarbonate solution (17 cm^3) at 0°C. The pH after the addition of the Oxone® solution was 7.25. The reaction was followed by GC / MS (Fisons MD-800; DD-1 25 m x 0.25 mm column, film thickness 0.25 μm; 10 minutes at 30°C, ramp at 20°C per minute to 150°C, held at 150°C for 30 minutes. Retention times: cyclohexene, 2.17 minutes; cyclohexene oxide, 7.24 minutes; cyclohexanone, 9.06 minutes; ketone **68**, 15.77 minutes).

The scale of this reaction was halved when ^{18}O labelled ketone was used as a promoter.

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